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Vol. XXVII NOVEMBER 1959 No. 5

CONTENTS

Editorial

Claude Bernard's Milieu Interieur Extended: Intracellular Acid-Base Relationships
EUGENE D. ROBIN AND PHILIP A. BROMBERG 689

Clinical Studies

Hyperbilirubinemia Due to an Alternate Path of Bilirubin Production
L. G. ISRAELS, H. J. SUDERMAN AND S. E. RITZMANN 693

In a study of unusual interest, the authors distinguish a form of familial hyperbilirubinemia in which the serum bilirubin level (predominantly unconjugated) and urinary and stool urobilinogen excretion were altogether out of proportion to the degree of ascertainable hemolysis, notably after splenectomy. These and other peculiarities suggest a congenital abnormality involving excessive bilirubin production from sources proximal in erythrogenesis to the mature circulating red cell ("shunt hyperbilirubinemia"). The argument is persuasive, and the accompanying remarks instructive.

A Survey for Hemagglutinins in Viral Hepatitis
ROBERT W. MCCOLLUM, VIGGO BECH, PETER ISACSON AND JOHN T. RIORDAN 703

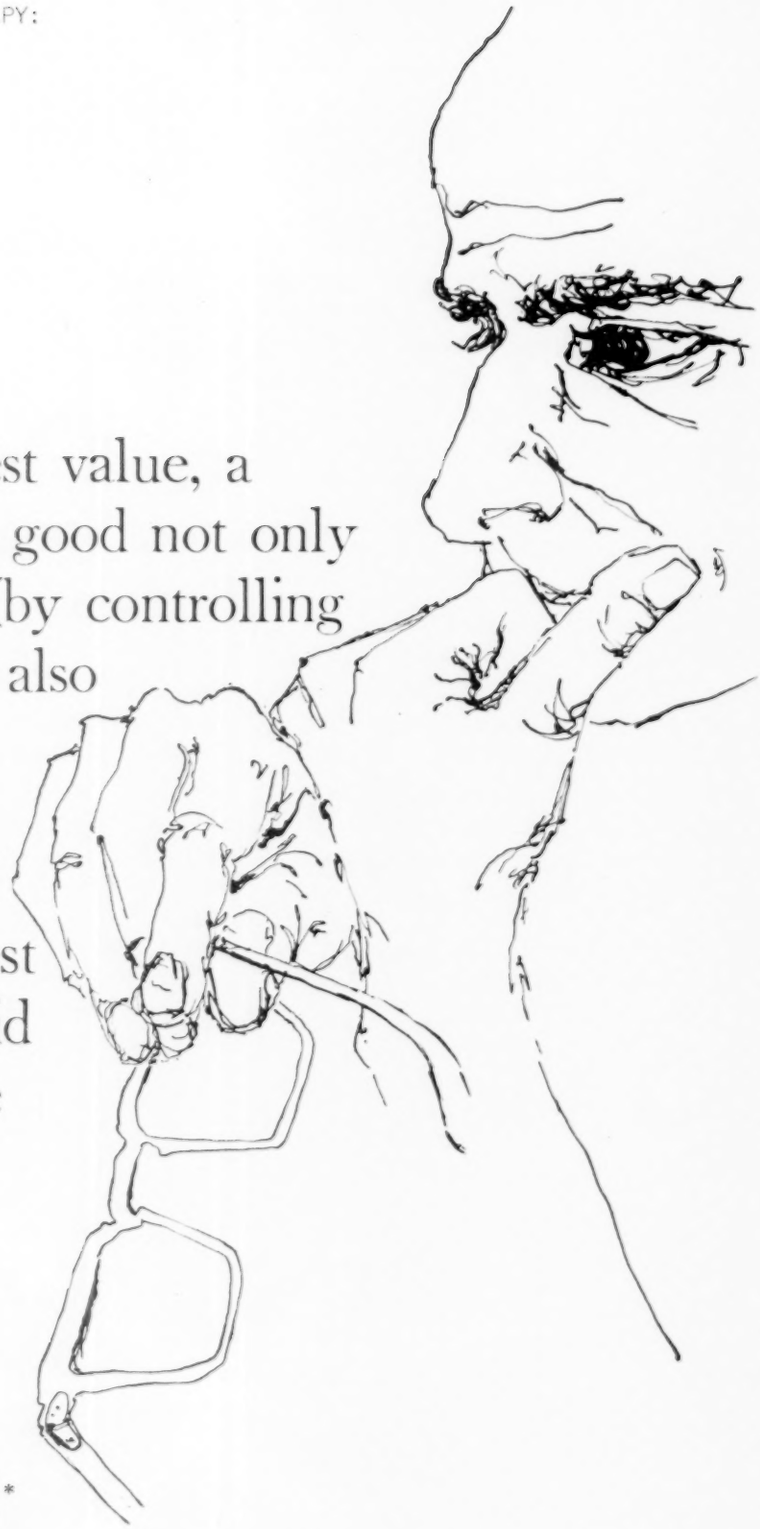
The need of a simple test to provide confirmation of the diagnosis in viral hepatitis is self-evident and, as this study indicates, some progress in this direction is being made. The rhesus erythrocyte agglutination test, which has been proposed for the purpose, was found wanting, giving positive results in many apparently normal human subjects, among others. The chick cell agglutination test, using acetone-ether extracted serum to lessen non-specific reactions, gave more hopeful results, but again not specific enough, except apparently in the differential diagnosis of jaundiced patients.

Liver Cell Necrosis in Chlorpromazine Jaundice (Allergic Cholangiolitis). A Serial Study of Twenty-Six Needle Biopsy Specimens in Nine Patients
SAMUEL ZELMAN 708

Cholestasis, with its related clinical and laboratory findings, is recognized as the most striking manifestation of chlorpromazine jaundice. However, as Dr. Zelman points out and abundantly documents in nine carefully studied cases, liver cell necrosis also is apt to be present, usually associated with a distinct rise in serum transaminases, particularly SGPT. The question raised by these findings is whether a more significant role should not be ascribed to liver cell necrosis (hepatitis) in the pathogenesis of jaundice due to chlorpromazine, at least in some instances. This question is instructively discussed.

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REFLECTION ON CORTICOTHERAPY:



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VOLUME TWENTY-SEVEN NUMBER FIVE

A Familial Study in Idiopathic Hemochromatosis
T. H. Bothwell, I. Cohen, O. L. Abrahams and S. M. Perold 730

Idiopathic hemochromatosis is suspected to be a genetically transmitted inborn error in iron metabolism but it must be admitted that studies of familial incidence are still too few to give firm support to this concept, plausible as it is. The present study of six affected families clearly indicates that such studies may be rewarding, particularly if in addition to serum iron determinations one also obtains liver biopsies. The authors make the important point that early detection of the disease in this way may prevent development of the full blown (and irreversible) manifestations of the disorder since a program of prophylactic venesection can be instituted in time.

The Pathology of Psittacosis. A Report of Two Cases with Hepatitis
Ellard M. Yow, J. Charles Brennan, Jane Preston and Samuel Levy 739

A turkey-borne epidemic of psittacosis is described, two infected subjects coming down with severe systemic disease which was fatal in one instance. In addition to the well recognized respiratory tract involvement, a "lower nephron nephrosis" was present in one case, and the two severely affected patients exhibited manifestations of liver parenchymal damage. The paper includes an informative general survey of the problem of psittacosis in this country.

Seminar on Mycotic Infections

North American Blastomycosis . . E. Richard Harrell and Arthur C. Curtis 750

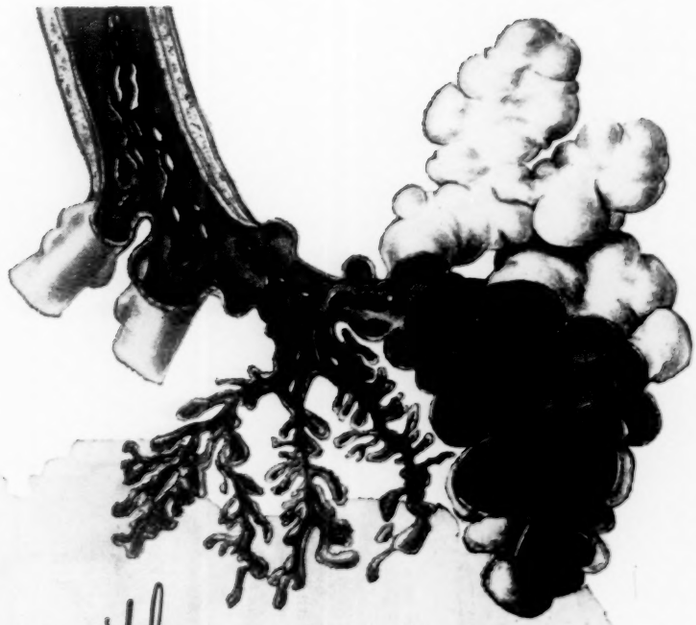
The authors begin with a general discussion of North American blastomycosis, following the more recent classification into systemic and primary cutaneous inoculation forms of the disease (most skin lesions being regarded as manifestations of disseminated, not primary infection). It is probable that, like coccidioidomycosis and histoplasmosis, the initial lesion in most cases is a mild pulmonary infection with non-specific respiratory symptoms. The most important recent development, however, is the use of amphotericin B, given intravenously, in treatment. As shown here, with eight illustrative cases, this agent is more effective than any hitherto available.

Combined Staff Clinic

Tranquilizing Drugs 767

Combined Staff Clinic (Columbia University College of Physicians & Surgeons)—It is not possible to do full justice to the large subject of tranquilizers, in all its ramifications, in one Clinic—there is neither sufficient space nor a sufficiency of statistically valid data. However, the present discussion will serve as a proper introduction, notably because, without losing sight of the great value of some of the drugs in question as agents for specific clinical management and for neuropharmacologic exploration, their indiscriminate use is vigorously decried and sound indications earnestly sought. After preliminary remarks for orientation in the mood of the Clinic, the various classes of drugs more or less appropriately designated tranquilizers are described, and current

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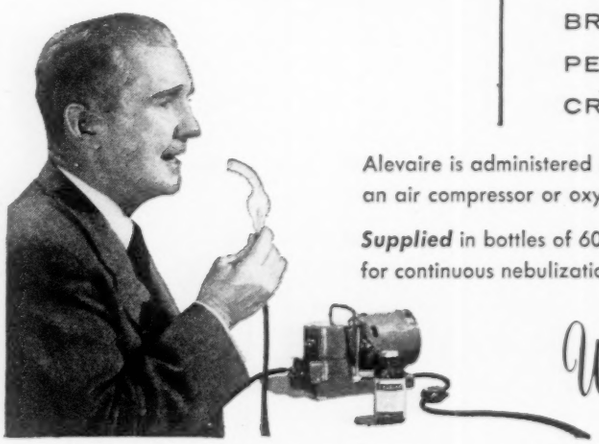
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VOLUME TWENTY-SEVEN NUMBER FIVE

views of their possible mode of action summarized. The usefulness of the phenothiazines specifically as antiemetics is evaluated, notably of perphenazine in Meniere's syndrome. The abuse of tranquilizers in general practice is then gently but firmly protested. Finally described are the extraordinary benefits of the phenothiazines and rauwolfia preparations in the management of psychotic patients who require hospitalization because of hyperactivity, excessive anxiety and tension or assaultiveness.

Case Reports

"Lowe's Syndrome." Abnormalities in Renal Tubular Function in Combination with Other Congenital Defects
EDGAR J. SCHOEN, WITH THE TECHNICAL ASSISTANCE OF GEORGE YOUNG 781

Two well studied cases corresponding to Lowe's syndrome are described, with special reference to abnormalities in renal tubular function which include features characteristic both of Fanconi syndrome and renal tubular acidosis.

Coarctation of the Abdominal Aorta with Stenosis of the Renal Arteries and Hypertension. Clinical and Pathologic Study of Two Cases and Review of the Literature
ALBERT A. BRUST, JOHN M. HOWARD, MILTON R. BRYANT AND JOHN T. GODWIN 793

Two cases of coarctation of the abdominal aorta are added to the fifteen previously reported instances of this congenital anomaly. The importance of renal artery stenosis secondary to a "jet" stream, and the possibility that the hypertension present is due to a Goldblatt mechanism is discussed. Clues to diagnosis are hypertension in a young person, without rib changes, with adequate peripheral pulse and the presence of an abnormal bruit. The importance of aortography in both diagnosis and evaluation of appropriate surgical correction is emphasized, but the danger of the procedure is well illustrated.

Lead Poisoning and Porphyria . . . JOHN T. GALAMBOS AND F. WILLIAM DOWDA 803

An interesting association, not as infrequent as might be supposed, and one which raises a number of questions.

Portal Venous Pressure in "Pipestem" Fibrosis of the Liver Due to Schistosomiasis
ARTHUR H. AUFSES, JR., FENTON SCHAFFNER, WILLIAM S. ROSENTHAL AND BERNARD E. HERMAN 807

The authors make an interesting point, that the portal hypertension of a patient with hepatic schistosomiasis was not associated with increased wedged hepatic vein (intrasinusoidal) pressure, as in true cirrhosis, hence dynamically was more closely related to obstruction of the extrahepatic portal vein. The observation supports the view that the "pipestem" portal fibrosis of schistosomiasis, which characteristically is not associated with the formation of regenerative nodules, does not constitute a true cirrhosis.

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CONTENTS continued–November 1959

VOLUME TWENTY-SEVEN NUMBER FIVE

Portal Hypertension Due to Schistosomiasis Mansoni
MARIO R. GARCIA-PALMIERI AND RAUL A. MARCIAL-ROJAS 811

An instructive case, again emphasizing the predominance of portal fibrosis and the minimum liver parenchymal involvement in schistosomal portal hypertension, as contrasted with portal hypertension in Laennec's cirrhosis.

Paraplegia, Hypokalemia and Nephropathy, with Muscle Lesions of Potassium Deficiency, Associated with Thyrotoxicosis
L. M. SANGHVI, K. D. GUPTA, K. BANERJEE AND K. BOSE 817

This well studied case presents a number of intriguing problems in interpretation of the relationships between thyrotoxicosis, muscle function and potassium metabolism.

Simultaneous Hyperthyroidism and Hyperparathyroidism
BOY FRAME AND ROBERT H. DURHAM 824

An interesting case.

Fabry's Disease (Angiokeratoma Corporis Diffusum Universale). An Unusual Syndrome with Multisystem Involvement and Unique Skin Manifestations
CAPT. WALTER J. KARR, JR. 829

An informative account of an interesting systemic disorder apparently representing a rare inborn error of lipid metabolism.

The Demonstration of Intranuclear Inclusion Bodies in Sputum from a Patient with Varicella Pneumonia . . . . BUERK WILLIAMS AND THOMAS H. CAPERS 836

An interesting demonstration in varicella pneumonia.

Jaundice Due to Prochlorperazine (Compazine)
FRANK A. SOLOMON, JR. AND FRANCIS A. CAMPAGNA 840

Jaundice due to administration of prochlorperazine must be exceedingly rare, but a case is described.

Hypokalemic Nephropathy in an Adrenalectomized Patient
JOHN F. WATSON AND FRED H. KATZ 844

A well studied case, interestingly discussed.

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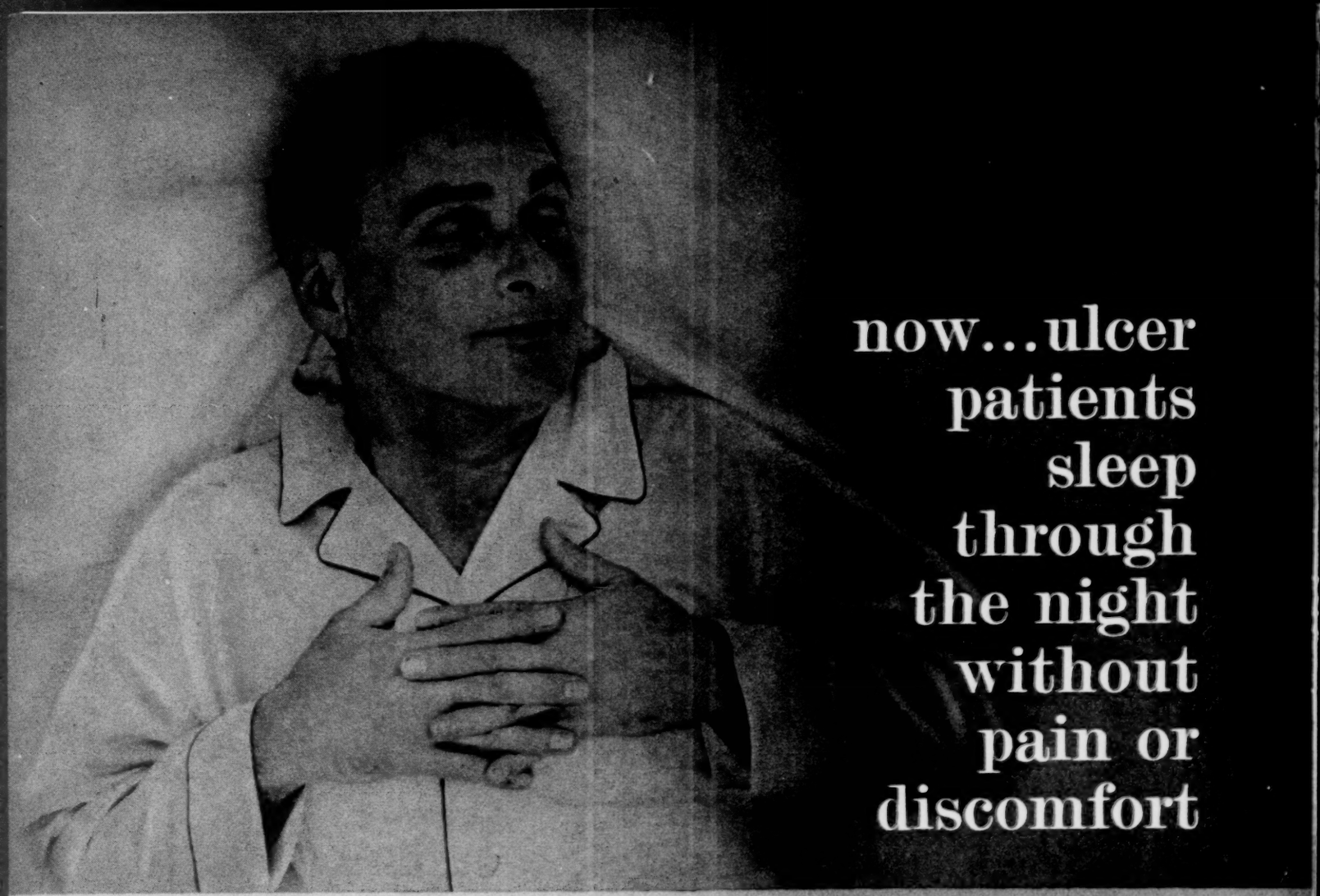
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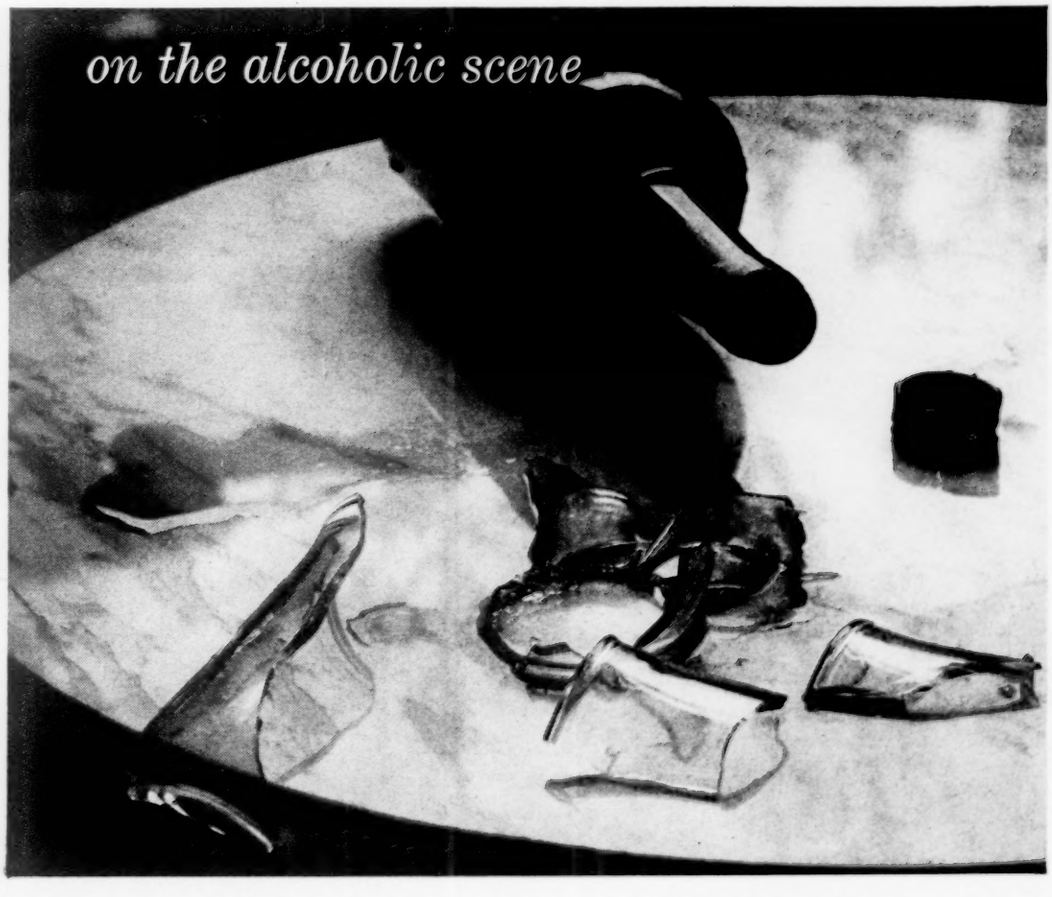
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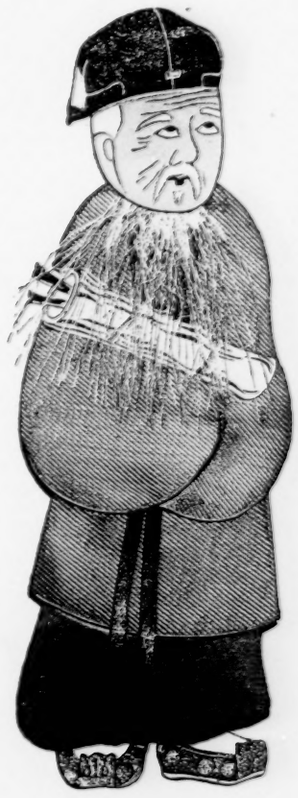
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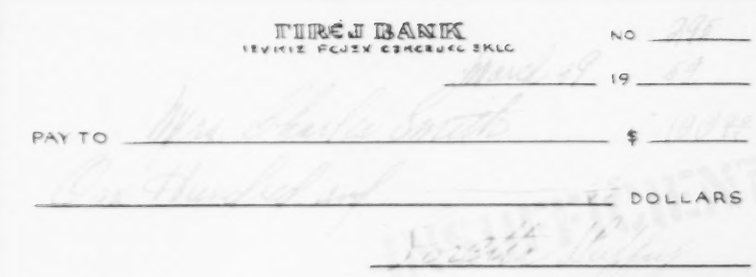
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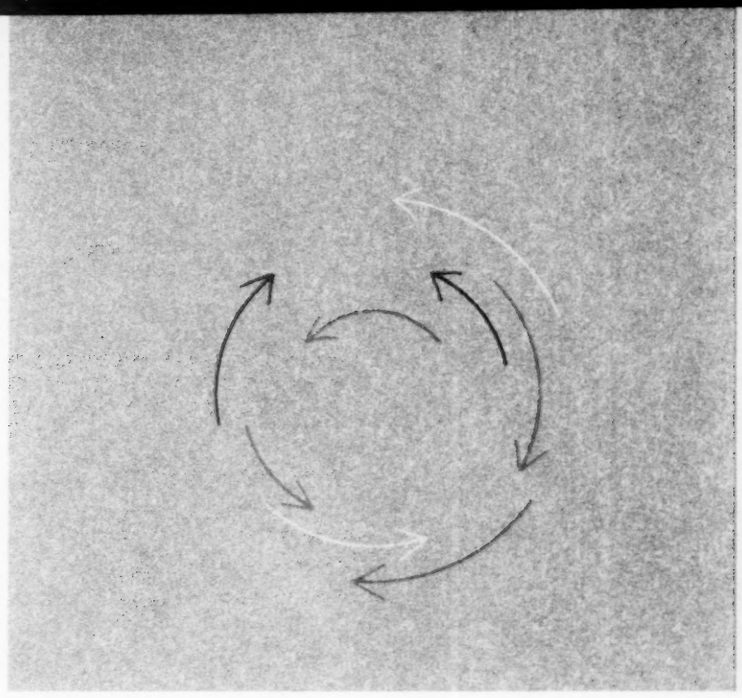
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LIVITAMIN®

with Peptonized Iron

...the preferred hematinic

*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition 1:35 (Jan.-Feb., 1957).

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NIAMID*

reduces pain in angina pectoris

NIAMID, in intensive clinical tests, has proved to have a high degree of safety and to be a valuable adjunct in the management of the anginal syndrome. NIAMID produces striking symptomatic improvement in angina patients...

- reduces frequency of anginal episodes
- diminishes severity of attacks
- decreases nitroglycerin requirements
- renews sense of well-being

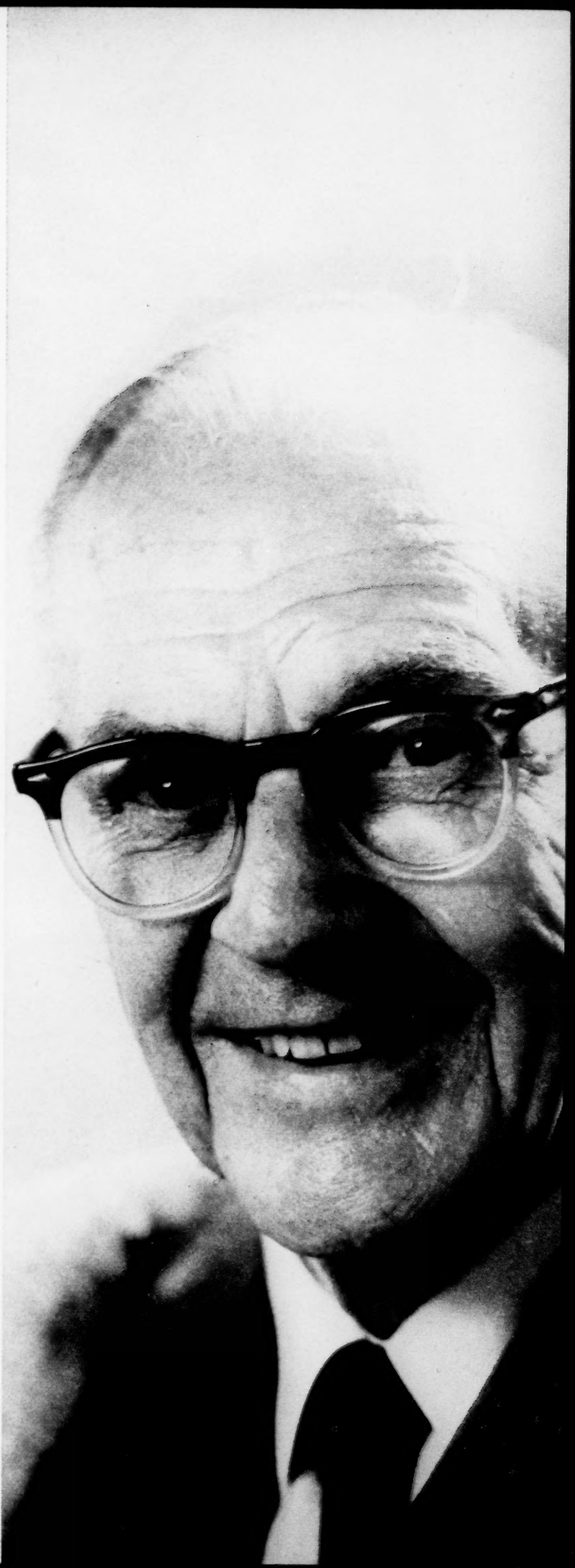
Note: Because of dramatic relief of symptoms and increased sense of well-being in anginal cases, it is advisable to caution the patient against overexertion.

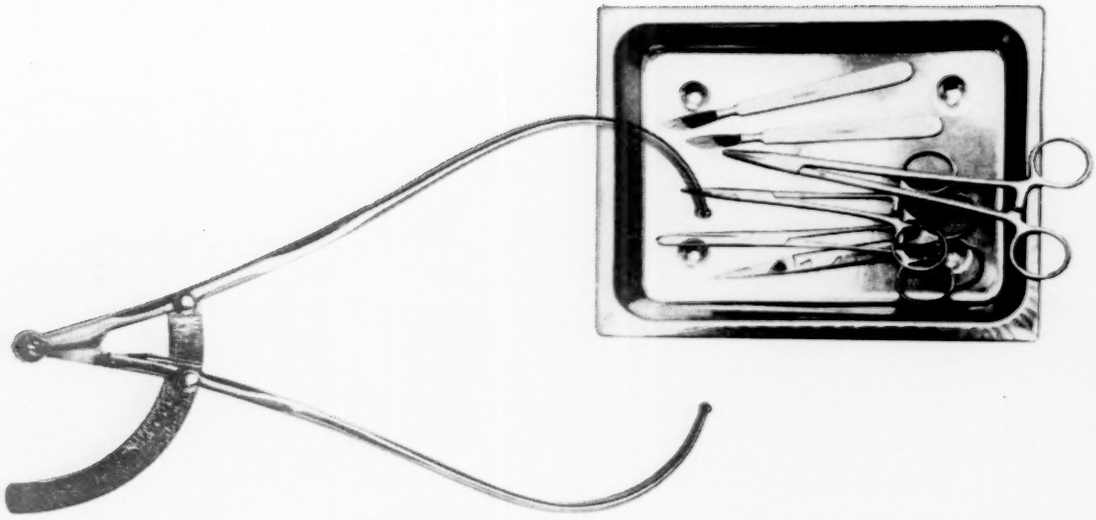
DOSAGE: Start with 75 mg. of NIAMID daily in single or divided doses. After 2 weeks or more, adjust the dosage, depending upon patient response, in steps of one or one-half 25 mg. tablet. Once improvement is seen, gradually reduce dosage to the maintenance level. Many patients respond to NIAMID within a few days, others within 7 to 14 days. NIAMID is available as 25 mg. (pink) and 100 mg. (orange) scored tablets.

A Professional Information Booklet giving detailed information on NIAMID *is available on request from the Medical Department, Pfizer Laboratories, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.*

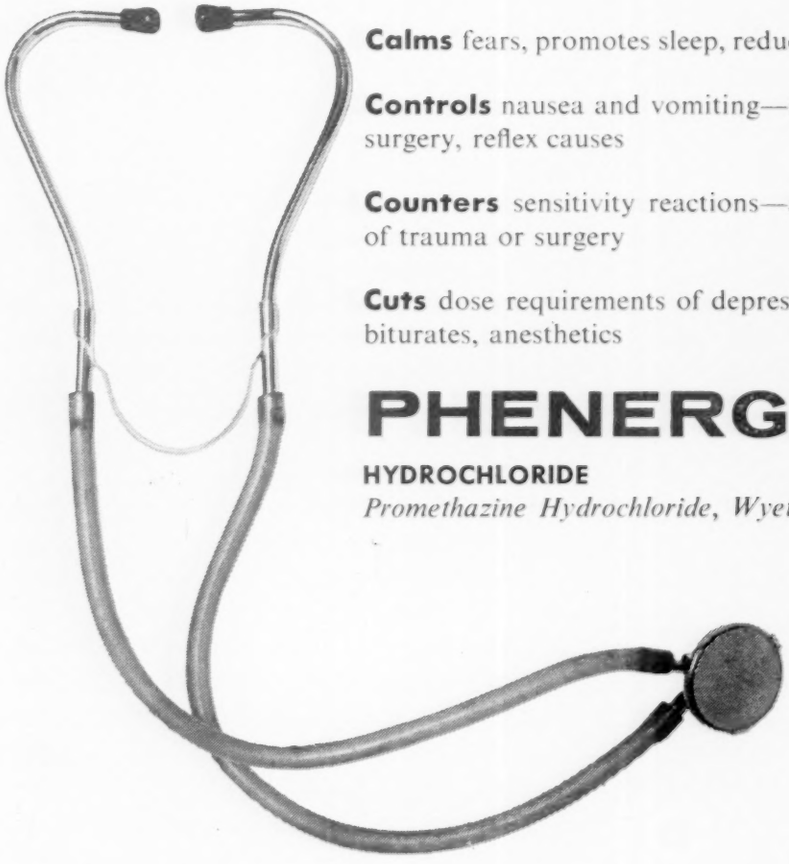
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Calms fears, promotes sleep, reduces postoperative excitement

Controls nausea and vomiting—motion sickness, pregnancy, surgery, reflex causes

Counters sensitivity reactions—allergy, drugs, tissue edema of trauma or surgery

Cuts dose requirements of depressant agents—narcotics, barbiturates, anesthetics

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for intra-articular and intrasynovial injection



for *longer* and *more pronounced* anti-inflammatory action in the *shortest time*

- when systemic therapy is contraindicated
- when systemic corticosteroids produce serious side effects
- to secure quick relief in one or two joints
- for use in conjunction with orthopedic procedures

Indications: rheumatoid arthritis; osteoarthritis; bursitis; peritendinitis; ganglion; intermittent hydroarthrosis; epicondylitis and related conditions.

ARISTOCORT Parenteral contains: 25 mg. per cc. of ARISTOCORT® Triamcinolone Diacetate micronized; polysorbate 80 U.S.P. 0.10%; benzyl alcohol 0.95%; benzalkonium chloride 0.01%; sorbitol solution N.F. 84.83%, and water for injection q.s. 100%.

All precautions required for intra-articular and intrasynovial administration of other corticosteroids should also be observed with ARISTOCORT Parenteral.

Complete information on dosage and administration is included in the package circular.

Supply: Vials of 5 cc. (25 mg. per cc.)

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Pectin (2 gr.)	142.8 mg.
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Atropine sulfate	0.0194 mg.
Hyoscine hydrobromide	0.0065 mg.
Phenobarbital (¼ gr.)	16.2 mg.

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Same formula, plus

Neomycin sulfate	300 mg.

(Equal to neomycin base, 210 mg.)

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Benadryl® hydrochloride (diphenhydramine hydrochloride, Parke-Davis)	56 mg.
Dihydrocodeinone bitartrate	⅙ gr.
Ammonium chloride	8 gr.
Potassium guaiacolsulfonate	8 gr.
Menthol	q.s.
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Supplied: Bottles of 16 ounces and 1 gallon.

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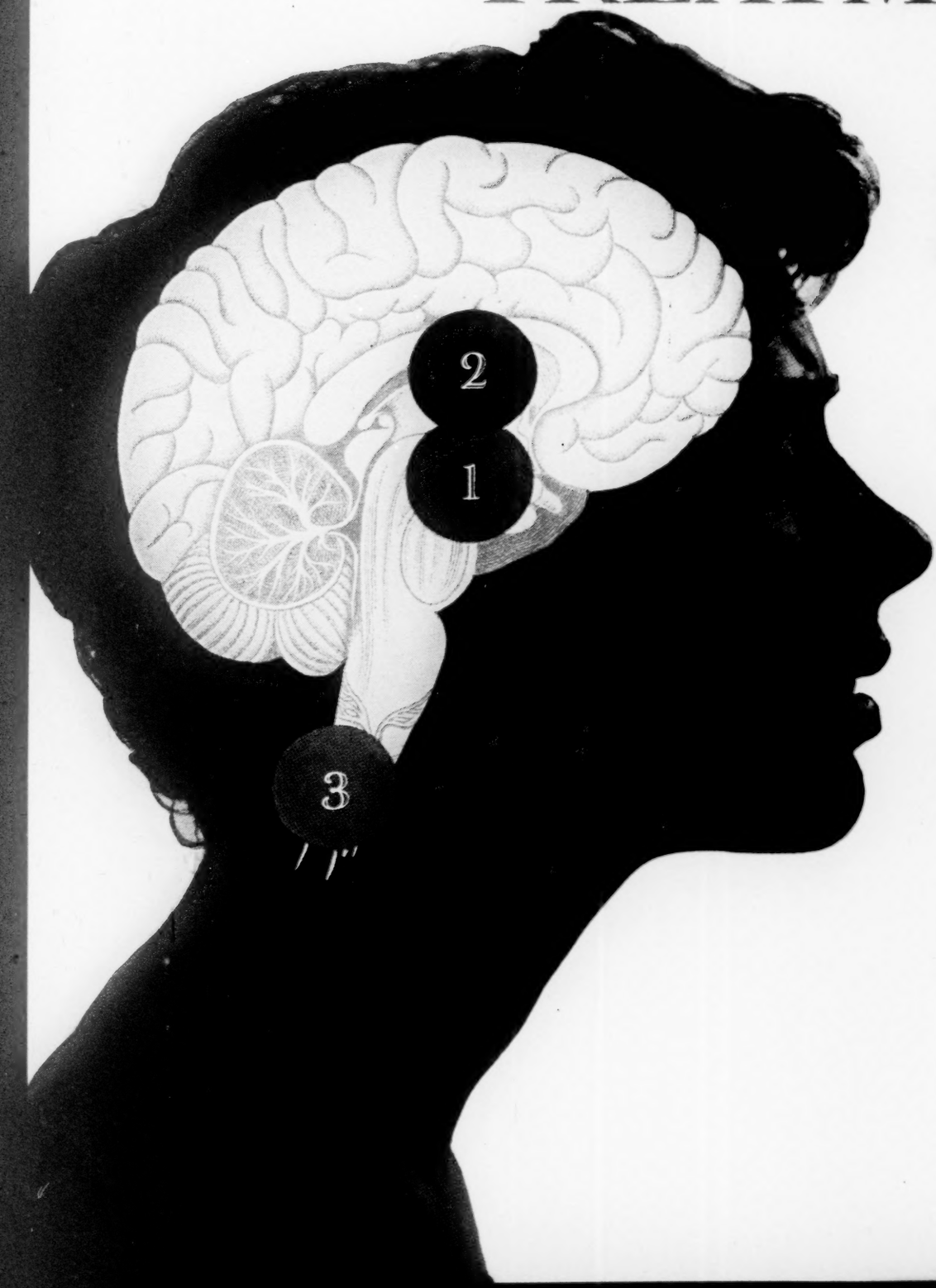
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FOR DEPRESSION

AND ASSOCIATED ANXIETY AND PHYSICAL TENSION

"Features of anxiety commonly accompany depressive features, and not infrequently these anxiety symptoms, not those of the underlying and primary depression, are the presenting ones."

Yonge, K.A.: Depressions in disguise. Canad. M.A.J. *74*:693, May 1, 1956.

RELIEVES DEPRESSION
by improving mood and outlook without excessive stimulation or rebound depression. Relieves symptoms such as crying, lethargy, loss of appetite, insomnia.

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by reducing exaggerated reaction at the seat of emotions. Does not depress cortical activity. Does not impair mental efficiency or normal behavior. No risk of drug-induced depression.

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by relaxing skeletal muscle. Aids restful sleep and reduces likelihood of symptom formation due to depression. Does not impair motor control.

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Supplied: Bottles of 50 light-pink, scored tablets.
Composition: Each tablet contains 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

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relieves painful muscle spasm, improves mobility, facilitates rehabilitation...

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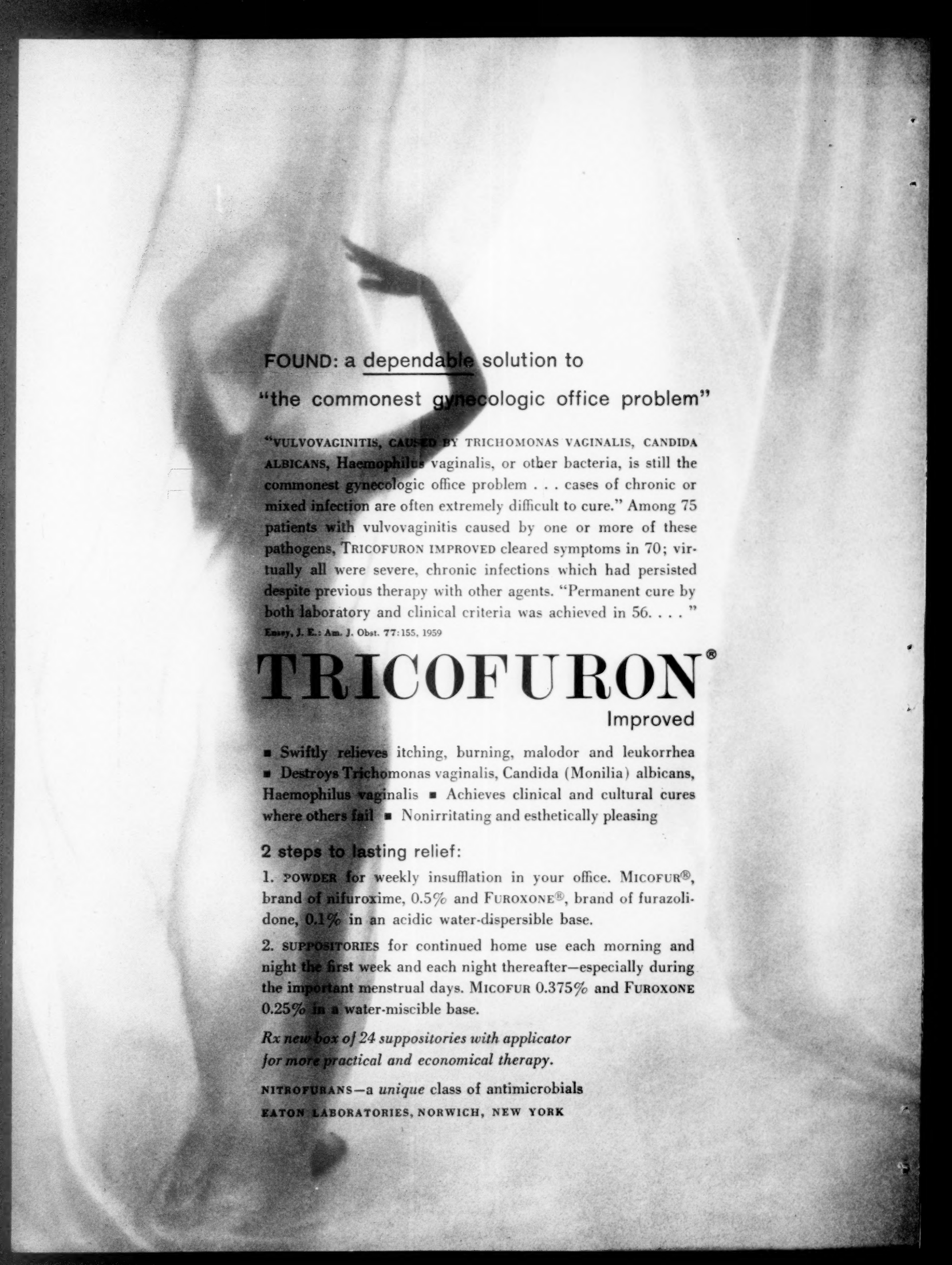
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Supplied: Tablets, scored, orange, bottles of 50. Each tablet contains PARAFLEX, 250 mg.

*U. S. Patent Pending 255A59



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Emery, J. E.: Am. J. Obst. 77:155, 1959

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non-narcotic—pain relief equivalent to that of codeine

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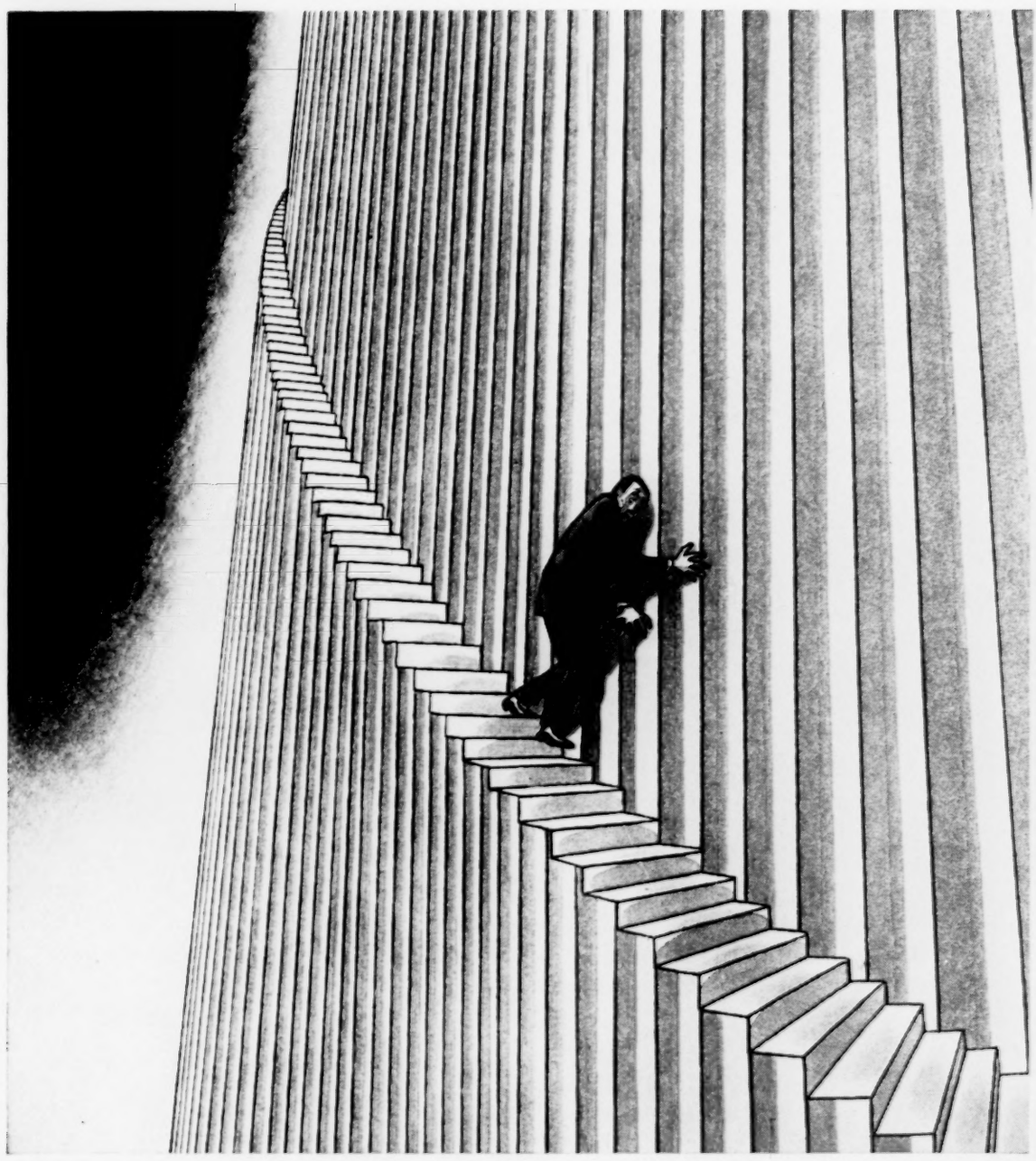
Supplied: Tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid.

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relieve the tension—and control its G.I. sequelae



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meprobamate with PATHILON® tridihexethyl chloride Lederle

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meprobamate (400 mg. or 200 mg.)—a tranquilizer and muscle-relaxant widely accepted for the effective management of tension and anxiety

PATHILON (25 mg.)—an anticholinergic long noted for producing prompt symptomatic relief through peripheral, atropine-like action, yet with few side effects

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for more flexible control of G. I. trauma and tension smooth, sugar-coated, easy-to-swallow

PATHIBAMATE-400 and PATHIBAMATE-200 are indicated for duodenal ulcer; gastric ulcer; intestinal colic; spastic and irritable colon; ileitis; esophageal spasm; anxiety neurosis with gastrointestinal symptoms and gastric hypermotility.

Supplied: PATHIBAMATE-400—Each tablet (yellow, 1/2-scored) contains meprobamate, 400 mg.; PATHILON tridihexethyl chloride 25 mg.

PATHIBAMATE-200—Each tablet (yellow, coated) contains meprobamate, 200 mg.; PATHILON tridihexethyl chloride, 25 mg.

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PATHIBAMATE-200—1 or 2 tablets three times a day at mealtime and 2 tablets at bedtime.

Adjust dosage to patient response.

Contraindications: glaucoma; pyloric obstruction, and obstruction of the urinary bladder neck.

Lederle LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

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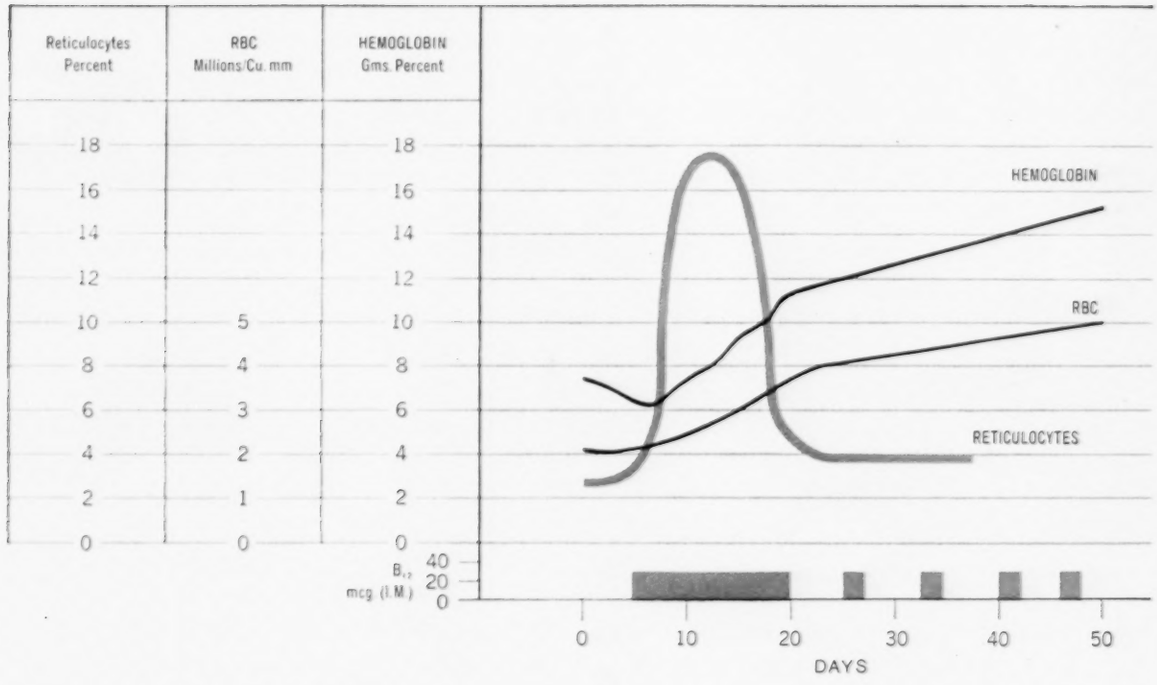
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RUBRAMIN PC is highly effective whenever high doses of vitamin B_{12} are required.



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Vitamin B_{12} is the therapeutic agent of choice in pernicious anemia, is effective in certain megaloblastic macrocytic anemias, and contributes to recovery or clinical improvement in a variety of neurological, liver and skin disorders.

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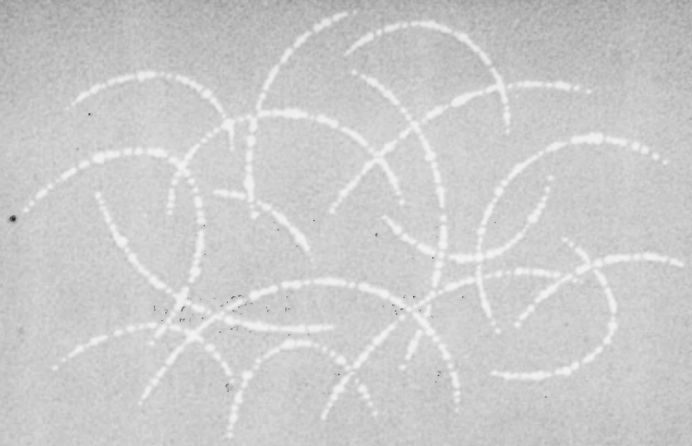
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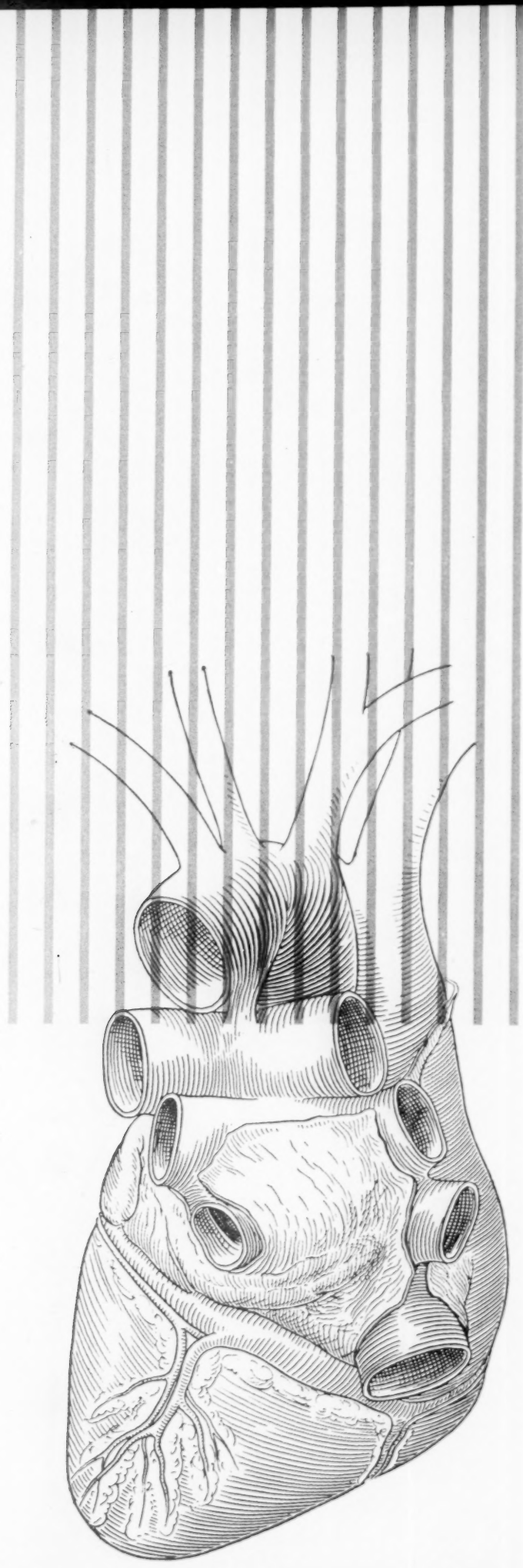
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Now, a single agent, important clinical

for total management of angina pectoris

Marplan prevents pain: Marplan is indicated primarily for patients with moderately severe to intractable angina pectoris. It has demonstrated a high degree of effectiveness. When used on a continuous dosage schedule, Marplan prevents pain, increases exercise tolerance and reduces nitroglycerin requirements.[1-3] To date, Marplan prophylaxis has been evaluated in over 300 angina patients. The response rate was 76 per cent with improvement ranging from a reduction in the number of attacks to virtual abolition of the anginal state.[1] One study reported "excellent effects with relatively small doses" and "greater relief than [with] any other compound in our experience."[2]

Marplan creates a more confident mental climate: Many angina patients display a more cheerful outlook when on Marplan therapy. This mental improvement is undoubtedly due to the antidepressive action of Marplan. However, it should be stressed that Marplan is indicated for *symptomatic* control of angina pectoris and, while it frequently abolishes anginal pain, Marplan does not appear to influence the EKG. Hence, as with previously available prophylactic agents, it is imperative that patients be instructed to maintain the same restriction of activity in force prior to Marplan therapy.

with two distinct primary effects, for two indications

Marplan

a happy balance of potency/safety

A broad clinical research program continues to define the full range of Marplan's clinical applicability. However, already some 300 research clinicians have evaluated Marplan in more than 4000 patients in two primary diagnostic categories—*angina pectoris and depression.*

Marplan has been shown to be considerably more active than other amine oxidase regulators. While clinically such increase in potency has heretofore been associated with increased side effects, Marplan strikes a happy balance of potency/safety. Marplan has shown markedly fewer of the side reactions of the hydrazines. Moreover, throughout the extensive clinical investigations, no liver damage has been reported. Marplan is an amine oxidase regulator, however, and like all of these agents, it is contraindicated in the presence of liver or kidney disease.

Consult complete literature and dosage instructions, available on request, before prescribing.

Bibliography: 1. Clinical reports on file, Roche Laboratories. 2. W. Hollander and R. W. Wilkins in J. H. Moyer, Ed., *Hypertension,* Philadelphia, W. B. Saunders Co., 1959, p. 399. 3. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 4. I. Kimbell, paper read at Co-operative Chemotherapy Studies in Psychiatry, 4th Annual Research Conference, Memphis, Tenn., May 20-22, 1959.

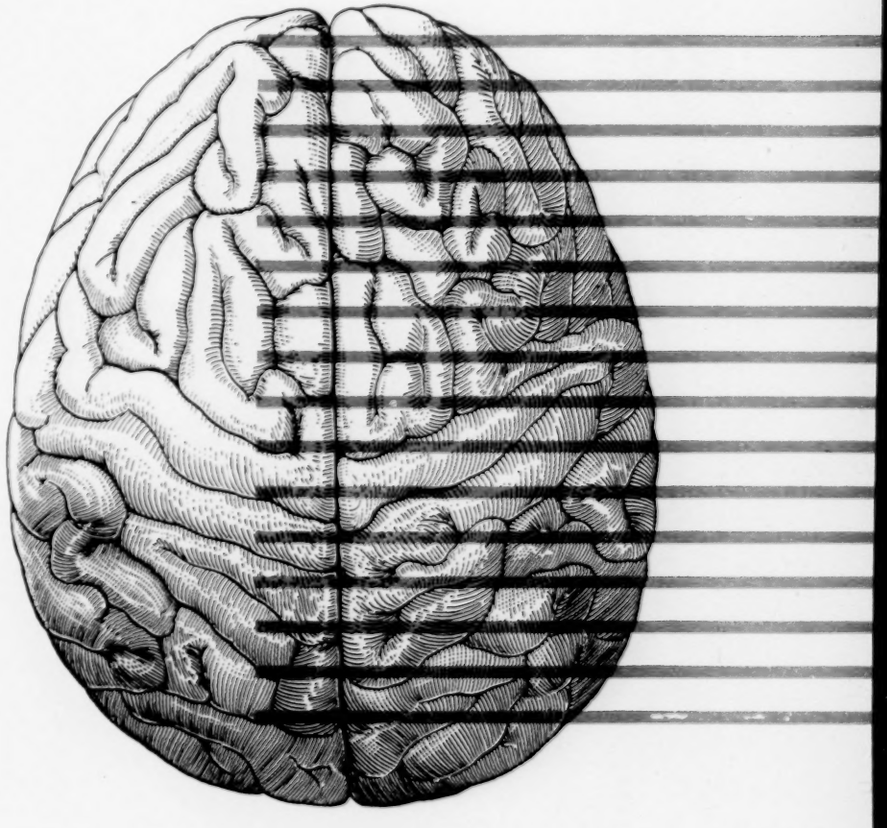
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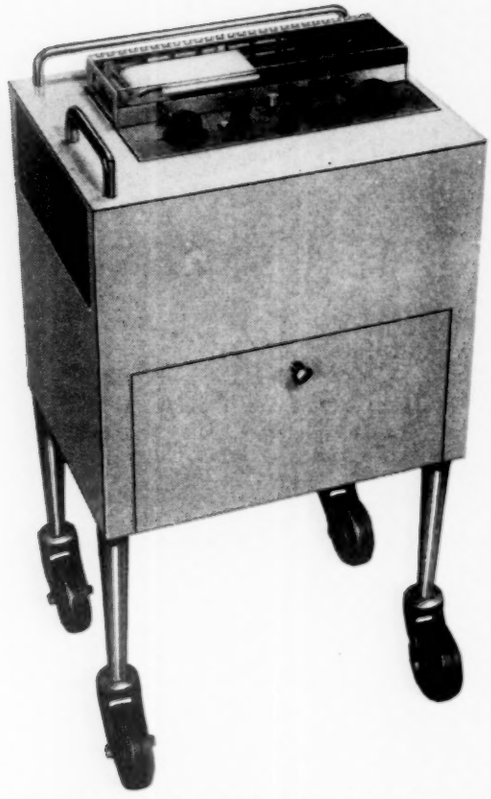
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Division of Hoffmann-La Roche Inc • Nutley 10 • N. J.

to lift depression

The value of Marplan in depression: Marplan is indicated in the broad range of emotional and psychiatric disorders with associated symptoms of depression, withdrawal or regression. To date, Marplan has been fully evaluated in more than 3700 patients with depression. The majority (67 per cent) showed significant improvement[1]: "Depression of mood and somatic preoccupation were less pronounced, concentration improved, irritability lessened, and the patients appeared to be more relaxed."[4]

Marplan in rheumatoid arthritis: Marplan has also been found to be valuable adjunctive therapy in the management of rheumatoid arthritis and other chronic debilitating disorders with associated depressed psychomotor activity.







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with 2 recording speeds • 3 sensitivities • provision for recording other waveforms • provision for visual monitoring

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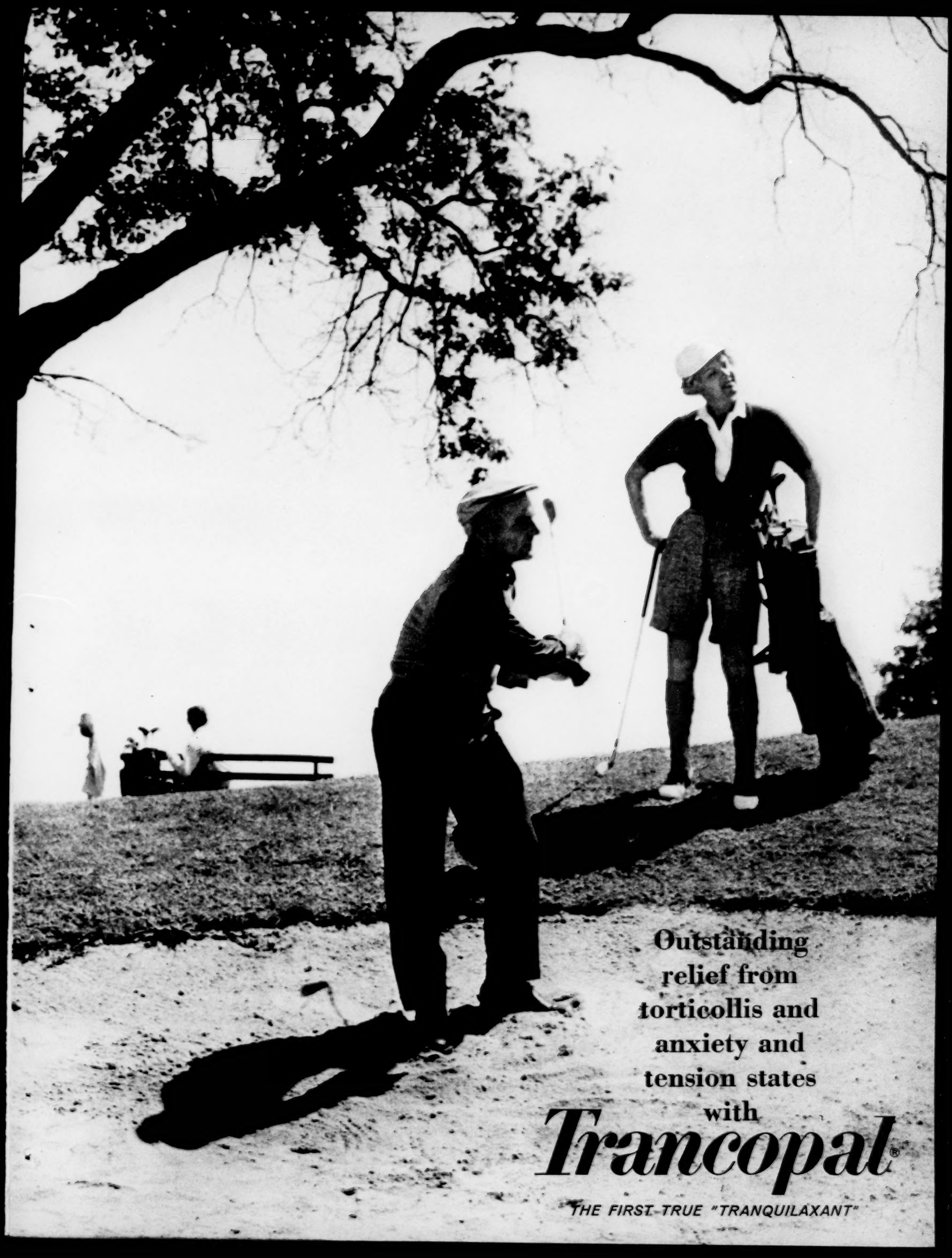


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THE FIRST TRUE "TRANQUILAXANT"

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for torticollis

A 55-year-old man complained of a painful, very stiff neck on the left side. There was marked muscle spasm that seemed to involve primarily the trapezius muscle. He had a severe headache, with the pain radiating down the left side of the neck to the shoulder. There were no other findings on physical examination and results of routine laboratory tests were normal.

Trancopal was prescribed in a dosage of 200 mg. q.i.d. The first and second dose of Trancopal gave only moderate relief. However, after the third dose, there was marked relief of the stiffness of the neck, as well as the headache and shoulder pain.

After the fourth dose, medication was gradually decreased and was discontinued on the sixth day. One week later, the patient had moderate recurrence of the torticollis, and Trancopal was again prescribed in doses of 200 mg. q.i.d. The patient obtained complete relief in one day and no further treatment was required.



THE FIRST TRUE "TRANQUILAXANT"

Trancopal®

for anxiety and tension states



case profile no. 3382*

A 35-year-old woman, a professional model, had an acute, severe attack of anxiety. She was irrational and unable to eat, and was very restless.

Initial medication consisted of aspirin with codeine and later meprobamate. Neither was effective, and the patient's condition became worse. She had to be hospitalized because of the marked anxiety. Trancopal was then prescribed in a dosage of 200 mg. q.i.d., in addition to bed rest.

After the second dose of 200 mg. of Trancopal, the patient became calm and rational, and was able to eat. The dosage of Trancopal was gradually reduced to 100 mg. q.i.d. on the fourth hospital day, after which the patient was discharged and was able to return to her normal occupation.

**Clinical Reports on file at the Department of Medical Research, Winthrop Laboratories.*

Turn page for complete listings of Indications and Dosage.

THE FIRST TRUE "TRANQUILAXANT"

Trancopal

potent MUSCLE RELAXANT
effective TRANQUILIZER

Indications:

Musculoskeletal[1]	Psychogenic[1]
Neck pain (torticollis, etc.)	Anxiety and tension states
Low back pain (lumbago, etc.)	Dysmenorrhea
Bursitis	Premenstrual tension
Rheumatoid arthritis	Asthma
Osteoarthritis	Angina pectoris
Disc syndrome	Alcoholism
Fibrositis	
Ankle sprain, tennis elbow, etc.	
Myositis	
Postoperative muscle spasm	

Dosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in fifteen to thirty minutes and lasts from four to six hours. The higher dosage is recommended for the treatment of patients in the acute stages of painful musculospastic conditions, and anxiety and tension states. Children (5 to 12 yrs.), 50 mg. three or four times daily.

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"Chlormethazanone [Trancopal] not only relieved painful muscle spasm, but allowed the patients to resume their normal activities with no interference in performance of either manual or intellectual tasks."[2]

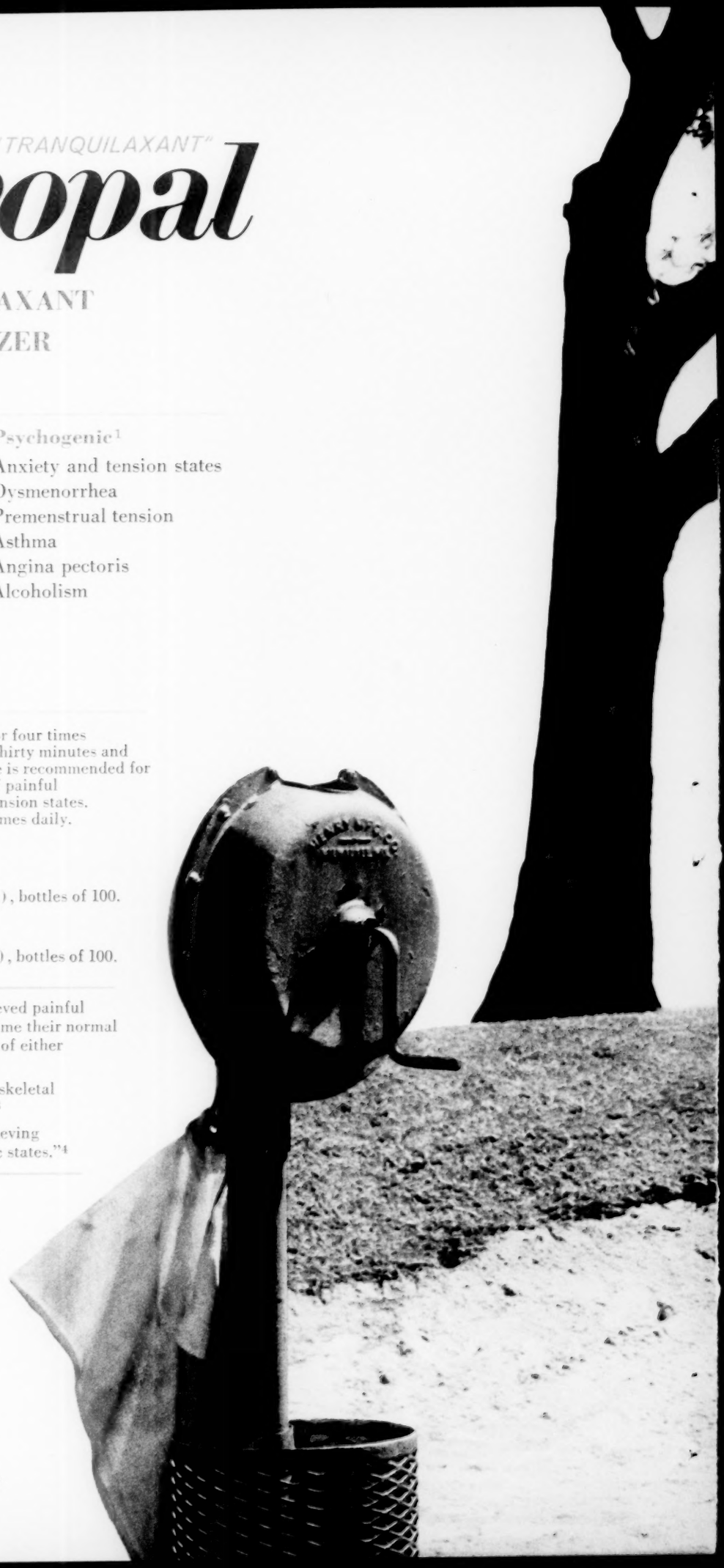
"The effect of this preparation in these cases [skeletal muscle spasm] was excellent and prompt . . ."[3]

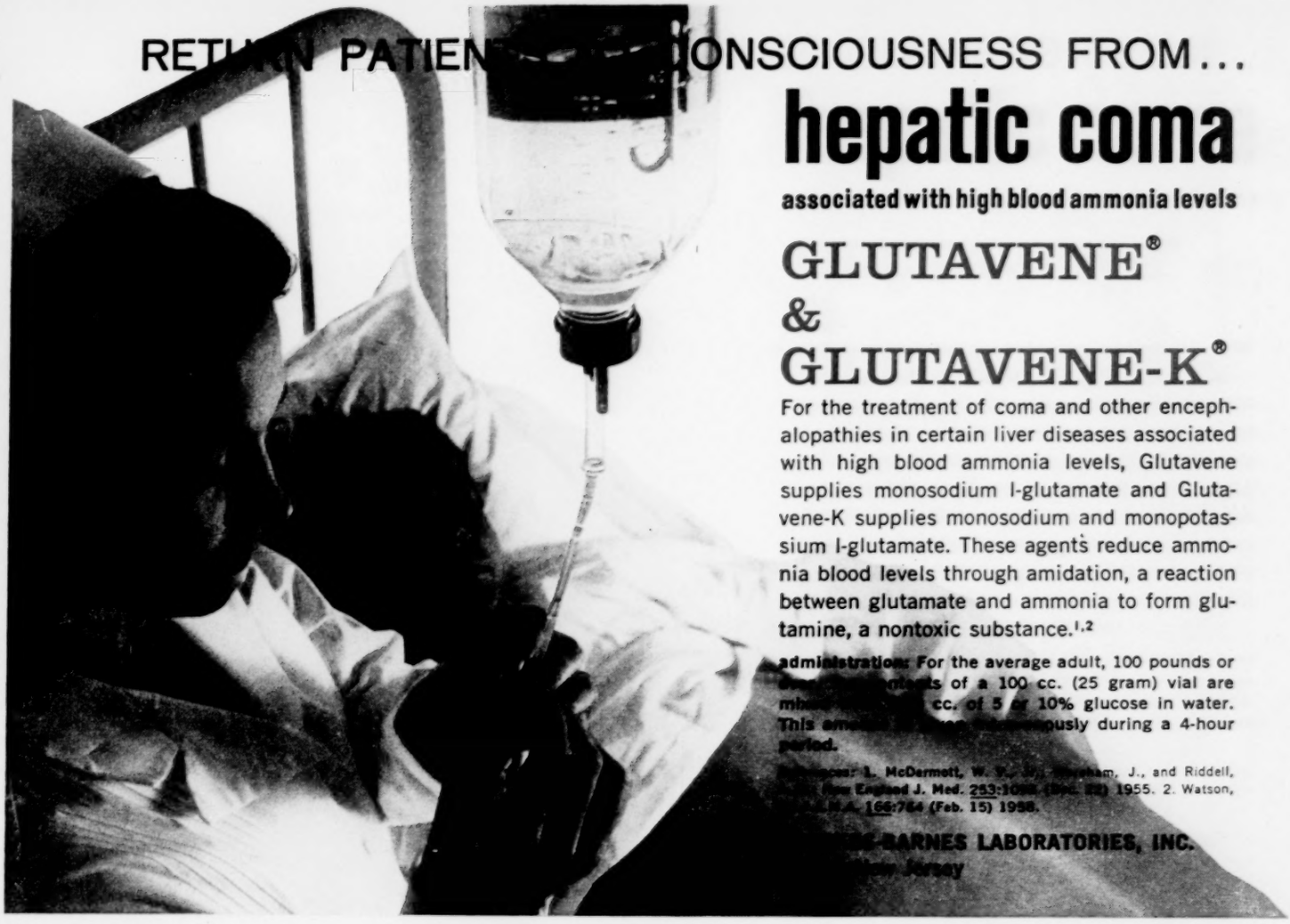
". . . Trancopal is a most valuable drug for relieving tension, apprehension and various psychogenic states."[4]

1. Collective Study, Department of Medical Research, Winthrop Laboratories.
2. Lichtman, A. L. (N.Y. Polyclinic M. Sch. & Hosp.): Kentucky Acad. Gen. Pract. J. 4:28, Oct., 1958.
3. Mullin, W. G., and Epifano, Leonard (Long Island College Hosp.): Am. Pract. & Digest Treat. To be published.
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[illegible]: L. McDermott, W. V. [illegible], Markham, J., and Riddell, [illegible] New England J. Med. 253:1088 (Dec. 22) 1955. 2. Watson, [illegible] J.A.M.A. 166:764 (Feb. 15) 1958.

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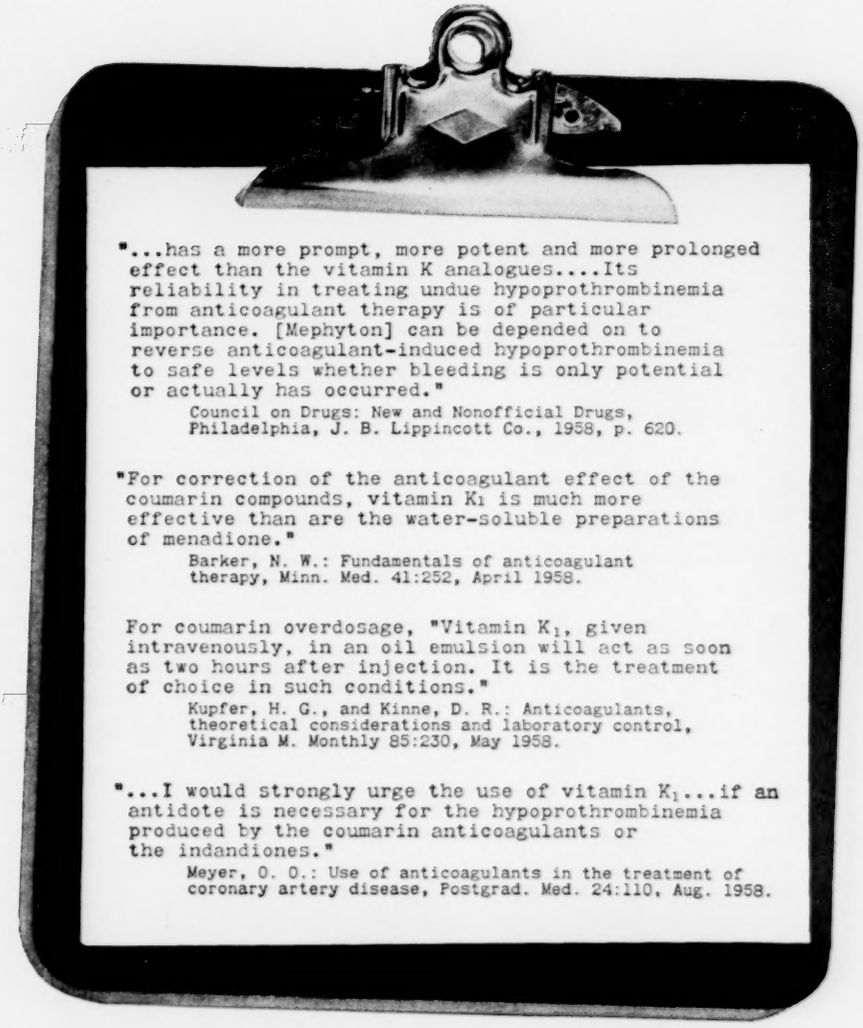
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Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1958, p. 620.

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Barker, N. W.: Fundamentals of anticoagulant therapy, Minn. Med. 41:252, April 1958.

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Kupfer, H. G., and Kinne, D. R.: Anticoagulants, theoretical considerations and laboratory control, Virginia M. Monthly 85:230, May 1958.

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Meyer, O. O.: Use of anticoagulants in the treatment of coronary artery disease, Postgrad. Med. 24:110, Aug. 1958.

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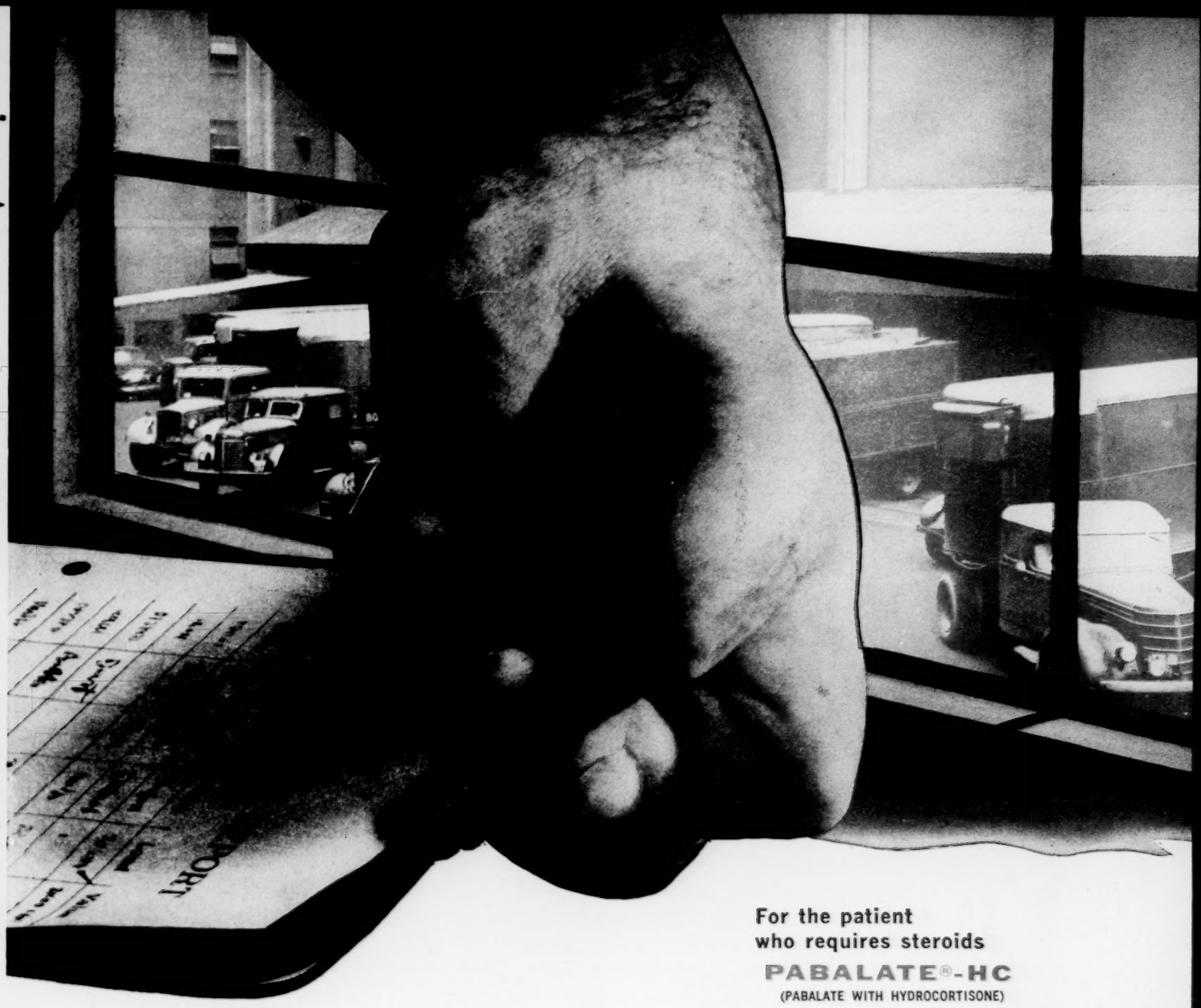


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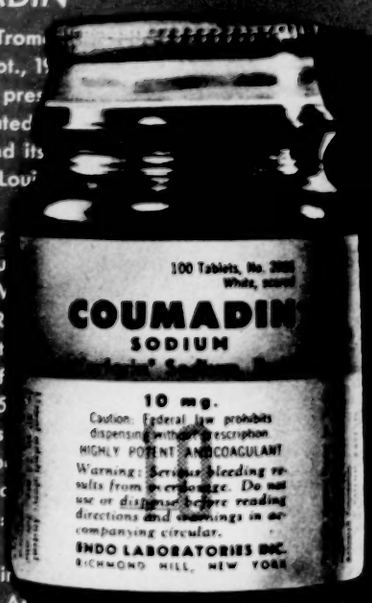
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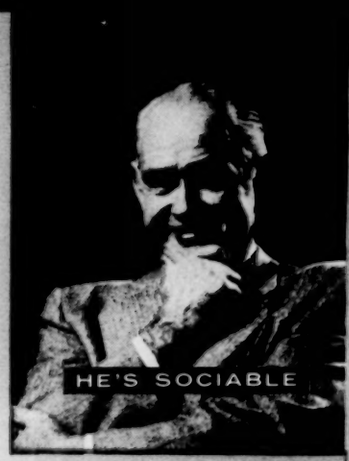
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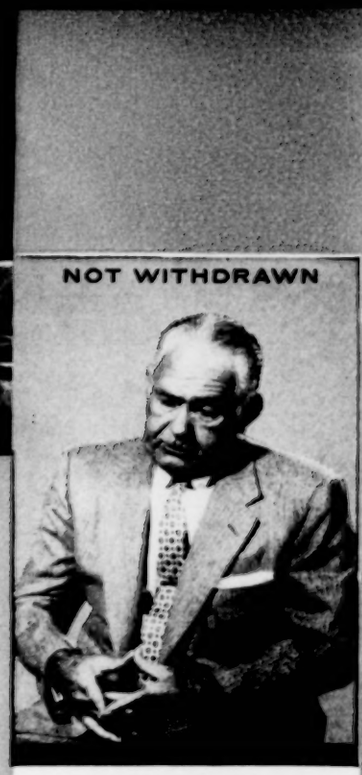
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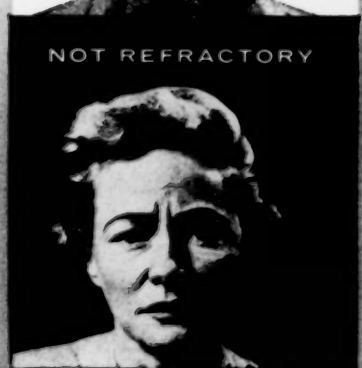
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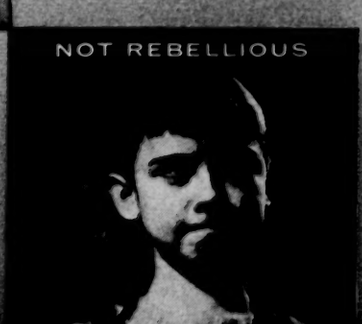












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Bloch, J., and Lenhardt, A.: Ann. New York Acad. Sc. 74:954, 1959.

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Lee, C. T., Jr.; Schless, G. L., and Duncan, G. G.: Ibid., p. 738

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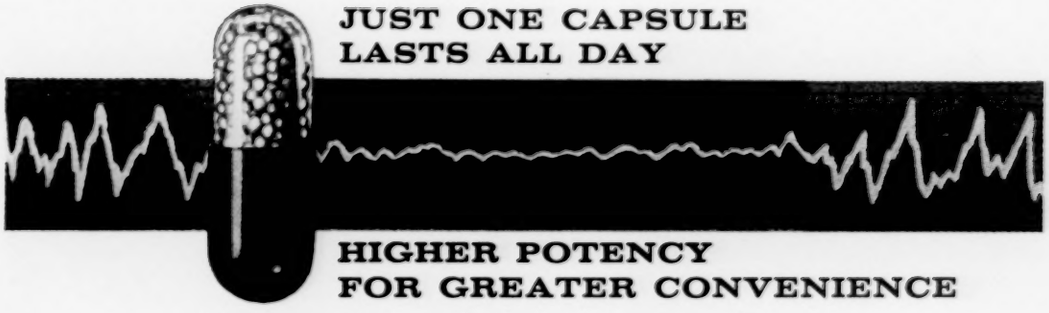
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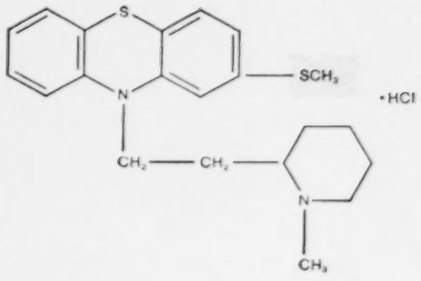
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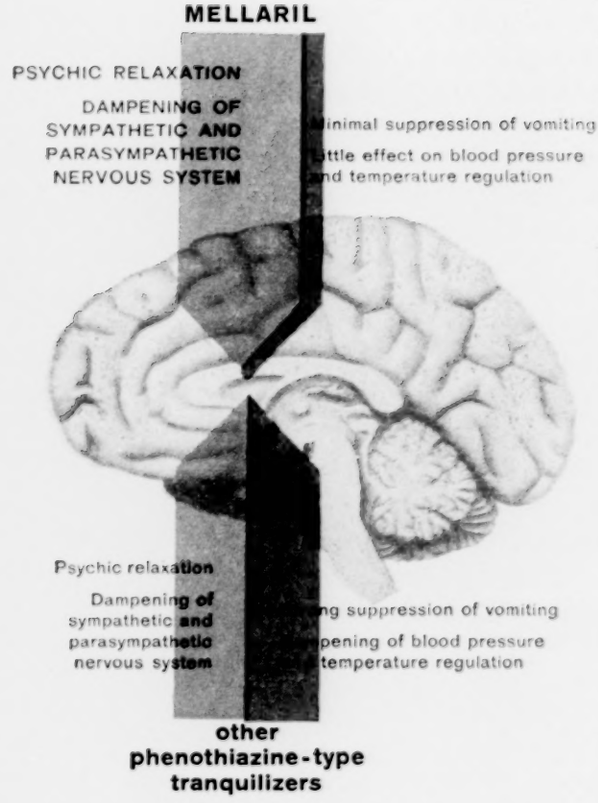
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*Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959.

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Proteus	5	5	*50.0*
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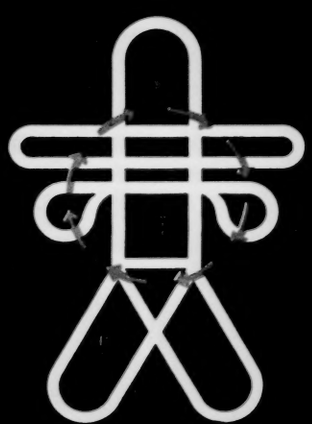
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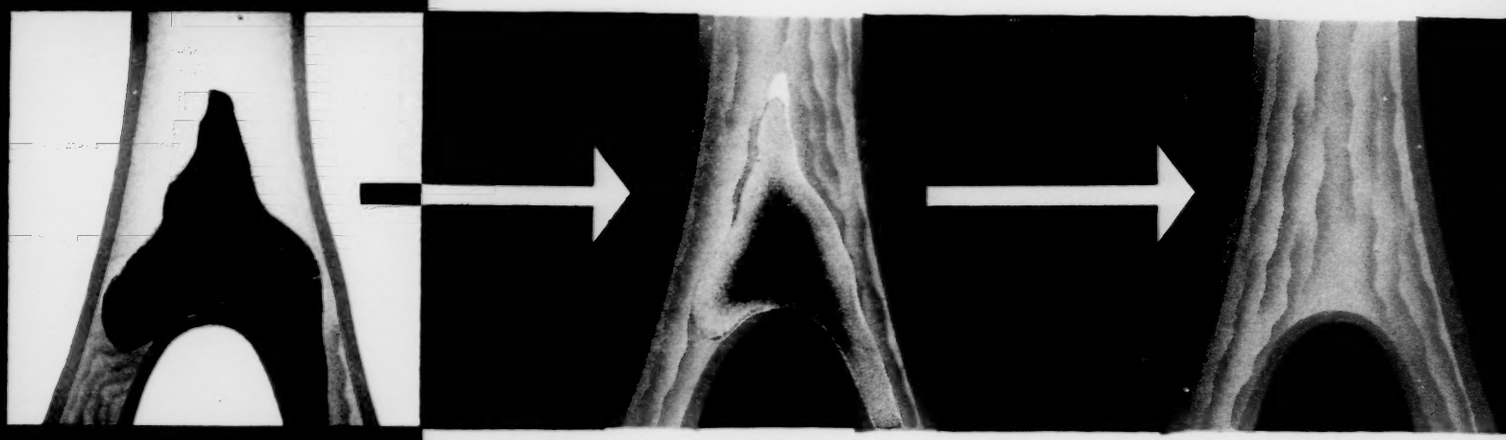
Fibrinolysin (Human)



3. Sussman, B.J.
4. Singher, H.O.

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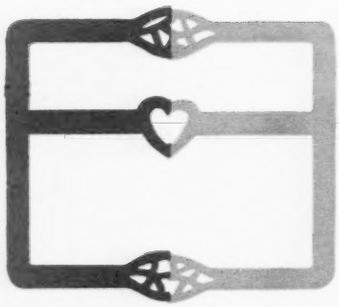
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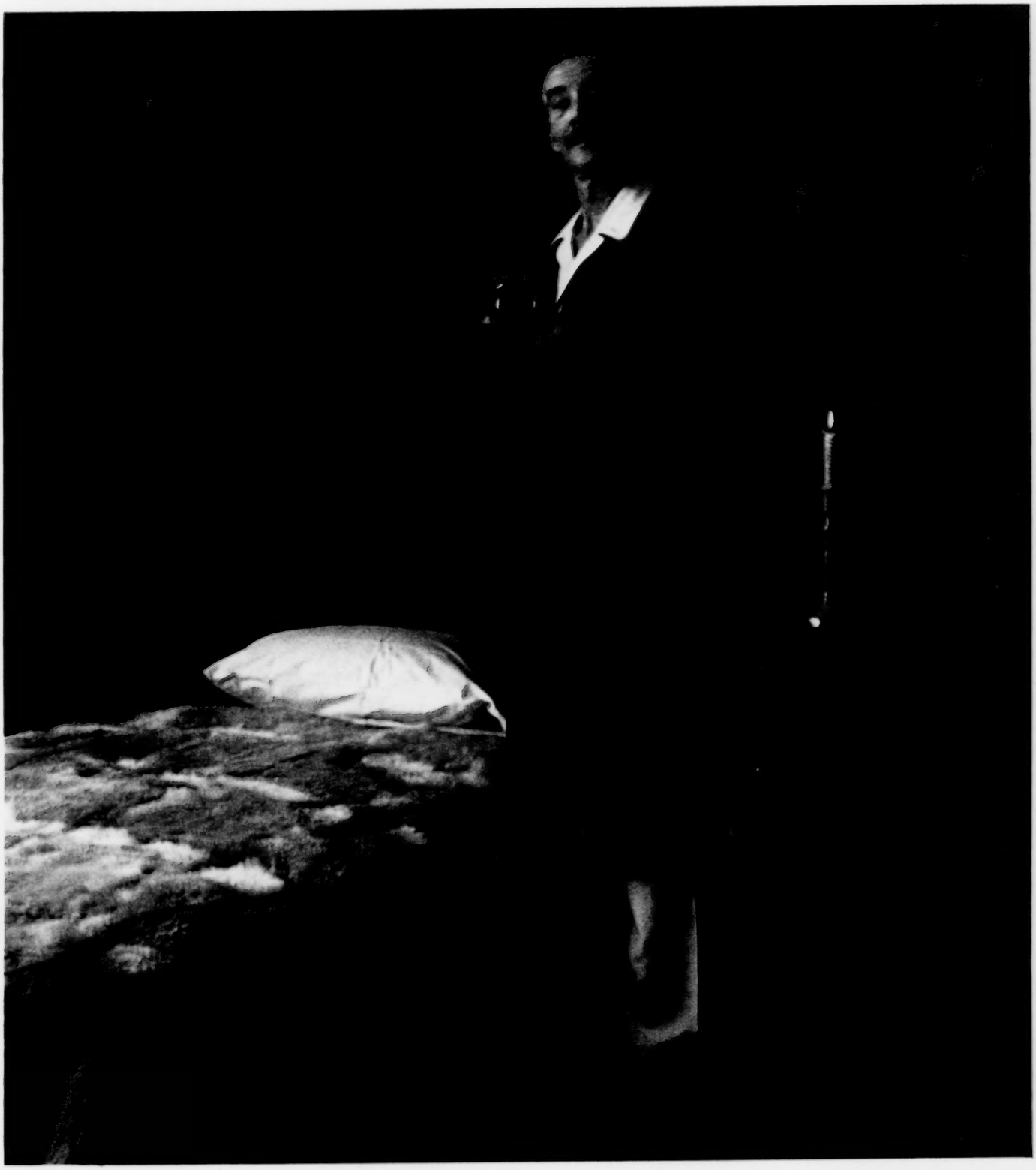
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The third investigator reports: "From our own clinical observations it would appear that deserpidine is the most desirable compound among those presently available."[3]

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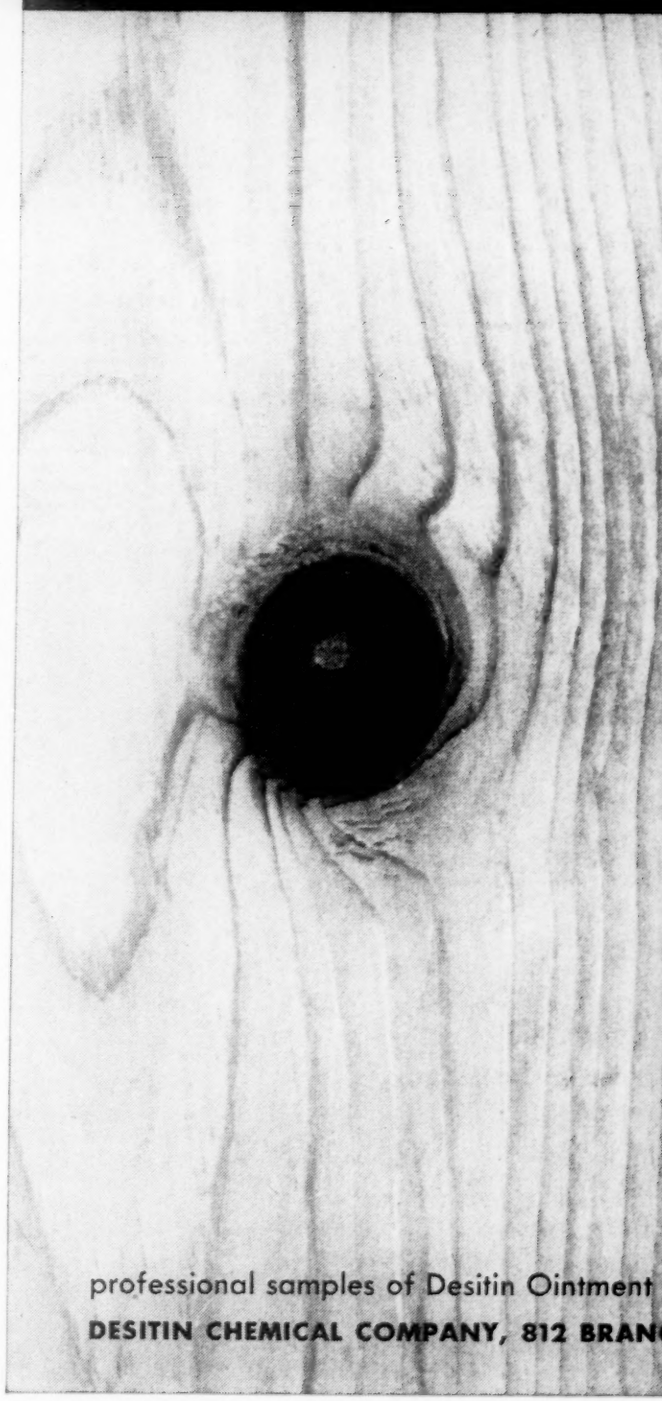
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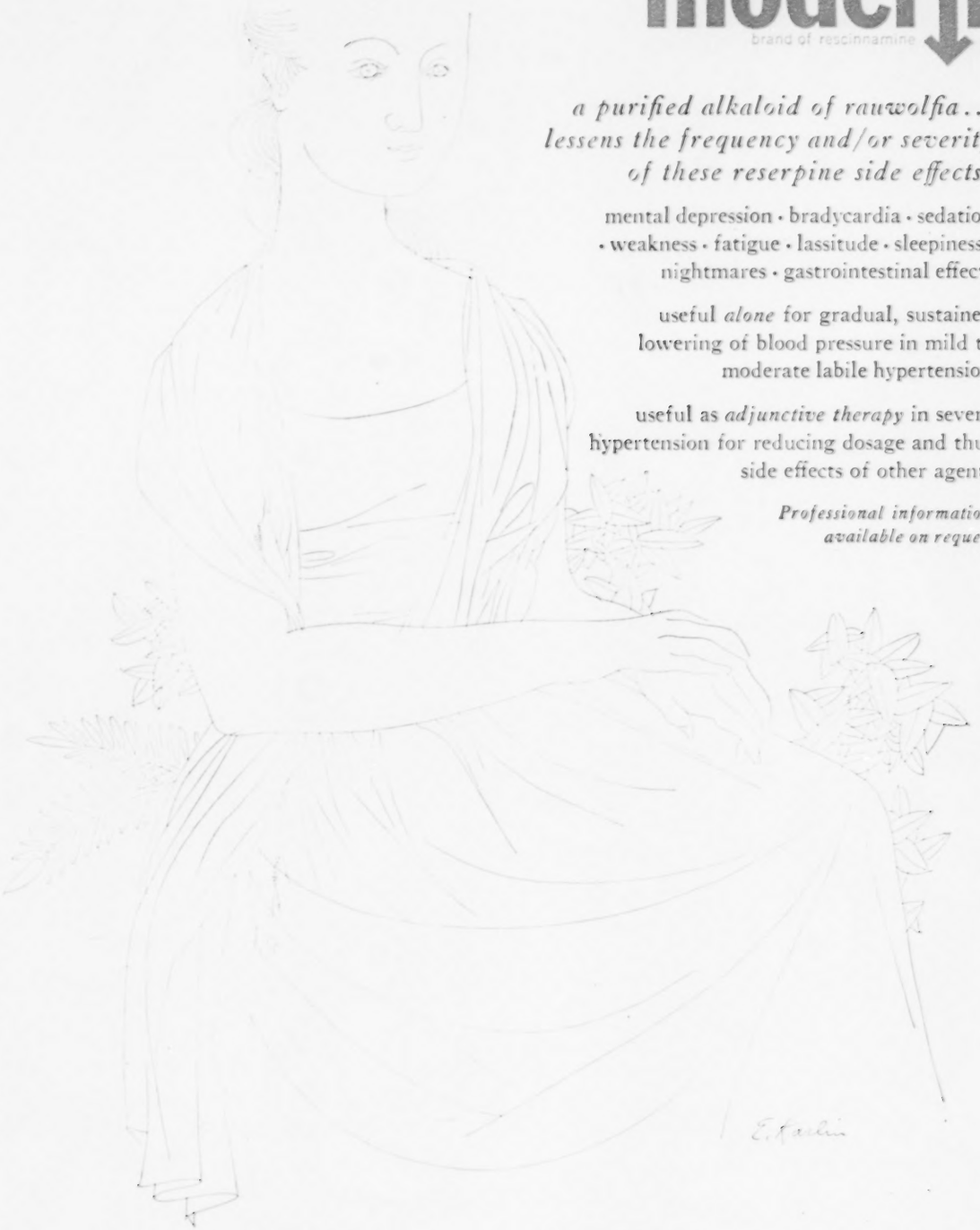
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The American Journal of Medicine

VOL. XXVII NOVEMBER, 1959 NO. 5

Editorial

Claude Bernard's Milieu Interieur Extended: Intracellular Acid-Base Relationships

IN 1850 Claude Bernard enunciated the doctrine of the constancy of the internal environment [*1*] as follows:

"The living organism does not really exist in the milieu exterieur (the atmosphere if it breathes, salt or fresh water if that is its element) but in the liquid milieu interieur formed by the circulating organic liquid which surrounds and bathes all the tissue elements; this is the lymph or plasma, the liquid part of the blood which, in the higher animals, is diffused through the tissues and forms the ensemble of the intracellular liquids and is the basis of all local nutrition and the common factor of all elementary exchanges.

"The stability of the milieu interieur is the primary condition for freedom and independence of existence; the mechanism which allows of this is that which ensures in the milieu interieur the maintenance of all the conditions necessary to the life of the elements."

Explicit in this doctrine was the concept that extracellular fluid constituted the internal environment of the organism. This doctrine has remained essentially unmodified for the past 100 years and has been validated by many physiologic studies. It has become one of the important conceptual cornerstones of modern biological science. However, recent work on acid-base relationships between the extracellular and intracellular compartments indicates that Claude Bernard's doctrine requires extension.

Investigations of the intracellular pH of isolated cells and isolated tissues over the past thirty-five years have provided consistent results. When the pH of the external media of such preparations is modified by the addition of hydrogen or bicarbonate ion, intracellular pH changes very little, if at all [*2–10*]. However, when the external pH is modified by certain specific acid-base substances, notably CO_2 gas, intracellular pH changes pari passu with extracellular pH [*11,12*]. Such studies have led to the conclusion that under many circumstances intracellular pH may be independent of extracellular pH.

Caldwell [*13*] has attributed the independence of intracellular pH to "the relatively small numbers of hydrogen ions and bicarbonate ions passing across the (cell) membrane(s), the small number of hydrogen ions being due to their small extracellular and intracellular concentrations and the small number of bicarbonate ions to permeability barriers."

Previous studies on intact animals appeared to give conflicting results. Wallace and Hastings [*14*] measured the changes in plasma and muscle pH of cats during extracellular metabolic acidosis produced by administration of hydrochloric acid and metabolic alkalosis produced by administration of sodium bicarbonate. Muscle bicarbonate remained relatively unchanged, despite marked changes in extracellular bicarbonate concentrations. They concluded that the muscle cell was "normally impermeable to bicarbonate ion," and clearly described the implications of this finding for the

over-all regulation of acid-base balance. These excellent studies have not been widely duplicated because of the technical difficulties involved in making direct measurements of CO_2 on tissue.

Apparently contradictory results have been obtained by several groups. The distribution of intravenously administered hydrochloric acid was studied in nephrectomized dogs by Swan and Pitts [*15*] and in dogs with intact kidneys by Schwartz, Orning and Porter [*16*]. Neither group could account for the administered H^+ solely on the basis of extracellular buffering. They concluded that H^+ ion was therefore buffered in the intracellular compartment. However, neither group made direct cellular estimations of bicarbonate ion, nor did they maintain CO_2 tensions at constant levels. The H^+ that could not be accounted for by extracellular buffering may well have penetrated certain special areas without over-all intracellular diffusion. An important area in this respect is bone. The active crystal lattice surfaces of bone act as an ion exchange mechanism, and it has been shown that bone serves as a vital site of buffering activity against metabolic acidosis [*17*]. These surfaces are, strictly speaking, neither extracellular nor intracellular, and exchange in such areas has been termed "transcellular exchange" [*18*]. Failure to consider such areas as a site of buffering in the absence of control of CO_2 tension would lead to an underestimate of the loss of hydrogen ion equivalents by the respiratory route. That this is probably the case is indicated by data [*19*] showing that when CO_2 tension is kept constant, equilibration of H^+ with the intracellular space is slower and less complete than described by these groups.

Swan, Axelrod, Seip and Pitts [*20*] administered sodium bicarbonate intravenously to nephrectomized dogs. They showed that approximately one-third of the injected bicarbonate disappeared from the extracellular space. It seemed possible that this fraction of bicarbonate was diffusing into the intracellular compartment. However, in these studies CO_2 tension likewise was not maintained at a constant level. Alternative explanations for the loss of bicarbonate from extracellular fluid include rapid diffusion into certain special areas of the intracellular compartment which are relatively permeable to bicarbonate (pancreas, bone); respiratory loss of CO_2 as CO_2 is generated from extracellular bicarbonate by reaction with extracellular buffers; and rapid diffusion of bicarbonate into cells generally, as CO_2.

Recently, two methods, independent of the CO_2-bicarbonate system, have been developed for specifically defining extracellular-intracellular acid-base relationships in intact animals. Both methods use the principle of non-ionic diffusion [*21*] for this purpose. Waddell and Butler [*22*] have used 5,5-dimethyl-2,4-oxazolidinedione (DMO), a weak acid, to investigate intracellular pH changes in the muscle of intact dogs. When extracellular pH was modified by increasing CO_2 tension, parallel changes took place in the intracellular pH of muscle. Hyperventilation produced a smaller increase in muscle pH than in extracellular pH, which was attributed to a difference in the CO_2 dissociation curves of plasma and muscle. When 7 mEq./kg. of hydrochloric acid was administered by vein, the blood pH fell by 0.36 units whereas the intracellular muscle pH fell by only 0.13 units. After the injection of an equivalent amount of sodium bicarbonate, the blood pH rose by 0.26 units while the muscle pH rose by only 0.04 pH units.

Robin, Bromberg and Forkner [*23*] have used the ammonia-ammonium buffer pair as a pH indicator system for investigating the relation between extracellular and mean whole body intracellular pH in the intact dog. By measuring total ammonium-ammonia concentrations in arterial plasma, they were able on a semiquantitative basis to determine the relative effect of a given procedure on extracellular-intracellular acid-base relationships. Their results indicate that the intracellular compartment is freely and rapidly permeable to CO_2 as a gas but that equilibrium with H^+ and HCO_3^- ions takes place only slowly.* Preliminary studies [*19*] indicate that the equilibration time of hydrogen ion penetration into cells is in excess of six hours.

These studies clearly confirm the early observations of the cellular physiologists, and it

* The term "slow equilibration" rather than the term "impermeability" is used advisedly. On the basis of ion size and ion charge, it would seem that cell membranes should be readily permeable to H^+ and HCO_3^-. It is not clear whether the independence of intracellular pH is based on total exclusion or on equal bidirectional movement of ions across cell membranes or on differences in buffering capacity of the two compartments. Evidence also exists that, given enough time (days), the intracellular compartment will come into equilibrium with the extracellular compartment in respect to HCO_3^- [*19*].

seems certain that intracellular pH may be quite independent of extracellular pH. The implications of these results for acid-base balance in the intact animal which are of great interest, can be illustrated by considering the acid-base relations of cerebrospinal fluid. Studies on the relationships between arterial plasma and spinal fluid reveal that spinal fluid, like much of the intracellular compartment, is freely permeable to CO_2 gas but that equilibrium with H^+ and HCO_3^- takes place slowly. As a result of this, in an animal with intact ventilation, the intravenous administration of hydrochloric acid produces arterial acidosis and a simultaneous shift of spinal fluid pH in an *alkaline* direction. The administration of sodium bicarbonate produces arterial alkalosis and a simultaneous shift of spinal fluid pH in an *acid* direction [*24*].

Thus it appears probable that, at least in acute states (for hours), mean whole body intracellular pH is independent of extracellular pH and indeed may shift in a completely opposite direction from extracellular pH!

This disparity between extracellular and intracellular pH suggests that for some functions it is useful to consider the organism as having not one but two kinds of internal environment—the *external* internal environment which is made up of extracellular fluid and the *internal* internal environment which each cell possesses inside its cell membrane. These two kinds of environment may differ markedly from each other. Major attention has been devoted to the external internal environment chiefly because it is relatively easy to approach, modify and measure. In reality, the internal internal environment may be the more important of the two. For example, most studies of acid-base balance have been conducted by modifying extracellular factors. Not only does acid production normally occur inside cells but also most forms of clinical acid-base disturbances are intracellular in origin. Under these circumstances, the extracellular compartment is affected only secondarily.

This approach to the internal environment also implies that a kind of "rugged individualism" is important in multicellular integrated function. It suggests that integrated multicellular function depends on a hierarchy of cellular function rather than on a common denominator of function furnished by extracellular fluid. It is more important for total body economy when the internal internal environment of a cell important in control mechanisms is modified by a given situation than is the case with a cell not involved in control mechanisms. For example, renal tubular cells containing an excess of hydrogen ions may excrete hydrogen ions despite coexistent severe extracellular alkalosis [*25*]. Heated hypothalamic cells cause vasodilation and increased skin blood flow even though the rest of the cells of the body are subjected to a cold environment [*26*]. The extracellular compartment serves chiefly as a form of communication or an integrating structure and not as the ultimate regulator of physiologic processes.

In the case of acid-base relations the problem is even more complicated since there is evidence that the distribution of hydrogen ions within the cell itself may not be uniform [*13*]. This nonuniformity may have profound consequences in terms of intracellular metabolic processes [*27*].

It seems probable that a consideration of the physiologic mechanisms subserving the function and control of the internal internal environment will prove to be an important area of future work.

EUGENE D. ROBIN, M.D.
University of Pittsburgh Medical School
Pittsburgh, Pennsylvania
and PHILIP A. BROMBERG, M.D.
Harvard Medical School
Boston, Massachusetts

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Clinical Studies

Hyperbilirubinemia Due to an Alternate Path of Bilirubin Production*

L. G. Israels, M.D., H. J. Suderman, M.Sc. *and* S. E. Ritzmann, M.D.
Winnipeg, Canada

Hyperbilirubinemia is the result of either increased production or inadequate removal of bilirubin. Inadequate removal of pigment may result from biliary obstruction, hepatocellular damage or a biochemical fault in the conjugation of bilirubin with glucuronic acid. Excess production of bilirubin is usually associated with hemolysis. Although bilirubin sources other than the circulating erythrocyte are known, they have rarely been implicated as a cause of jaundice.

The study to be described is that of four cases of jaundice occurring in two Mennonite families from Southern Manitoba. The affected members exhibited hyperbilirubinemia which could not be directly related to the excessive breakdown of circulating erythrocytes or to a defect in their hepatic conjugation mechanism. It is thought that these patients have a congenital abnormality characterized by excessive production of bile pigment from sources other than the circulating red cells. A fifth case of hyperbilirubinemia due to primary overproduction of pigment complicating liver disease is also described.

EXPERIMENTAL METHODS AND RESULTS

Osmotic Fragility, Autohemolysis, Mechanical Fragility. These were performed according to the technics described by Dacie [*1*].

Urinary and Fecal Urobilinogen. The quantitative method of Schwartz, Sborov and Watson [*2*] was employed.

Red Cell Survival. Radioactive sodium chromate (Cr^{51}) was employed. The normal T/2 in our laboratory is twenty-eight to thirty-two days.

Bilirubin Clearance and Glucuronide Formation. The finding of an elevated indirect reacting bilirubin in the absence of hemolysis suggested the possibility of a defect in bilirubin clearance or glucuronide synthesis. Accordingly, the following tests were carried out:

Bilirubin excretion test: Fifty milligrams of pure bilirubin (Homburg) was injected intravenously and blood samples were drawn at three minutes and at one, two and three hours after the injection. The three-minute value was taken as 100 per cent and the per cent retention at three hours calculated from this value. This is based on the methods of Eilbott [*3*] and Von Bergmann [*4*]. Normal retention is less than 15 per cent at three hours.

Glucuronide formation: The rate of glucuronide formation was examined in three patients according to the method outlined by Axelrod, Schmid and Hammaker [*5*]. Following the oral administration of 22 to 25 mg. of p-hydroxyacetanilide (Eastman) per kg. body weight, venous blood was taken at suitable intervals up to nine hours. Aliquots of 2 or 3 ml. of serum were analyzed for free p-hydroxyacetanilide by the procedure of Brodie and Axelrod [*6*]. Further aliquots of 3 ml. were treated with 1,000 units of bacterial β-glucuronidase (Sigma or Mann) suspended in 0.2 M, pH 6.0, acetate buffer and the mixtures incubated for three hours at 37°C. The total p-hydroxyacetanilide in the incubated mixtures was then determined and the glucuronide concentration calculated from the difference between total and free values. Two patients (Cases II and III) conjugated the p-hydroxyacetanilide at a rate equivalent to the normal control and to the published curve of Axelrod et al. [*5*]. However, one patient (Case IV) exhibited a reduced rate of glucuronide formation. (Fig. 1.)

Tetrapyrrole Component of Hemoglobin. Consideration was also given to the possibility of an abnormal tetrapyrrole component of the hemoglobin of these patients which might alter the red cell, bring about its destruction, and subsequently give rise to an abnormal bilirubin which could be excreted only with difficulty. The hemoglobin and bilirubin of three of the jaundiced patients (Cases I, II and III) were examined by the following methods:

Paper electrophoresis of hemoglobin: This was performed on stroma-free hemoglobin solutions on

* From the Departments of Medicine and Biochemistry, University of Manitoba, Winnipeg, Canada. This study was supported by a grant from the National Cancer Institute of Canada.

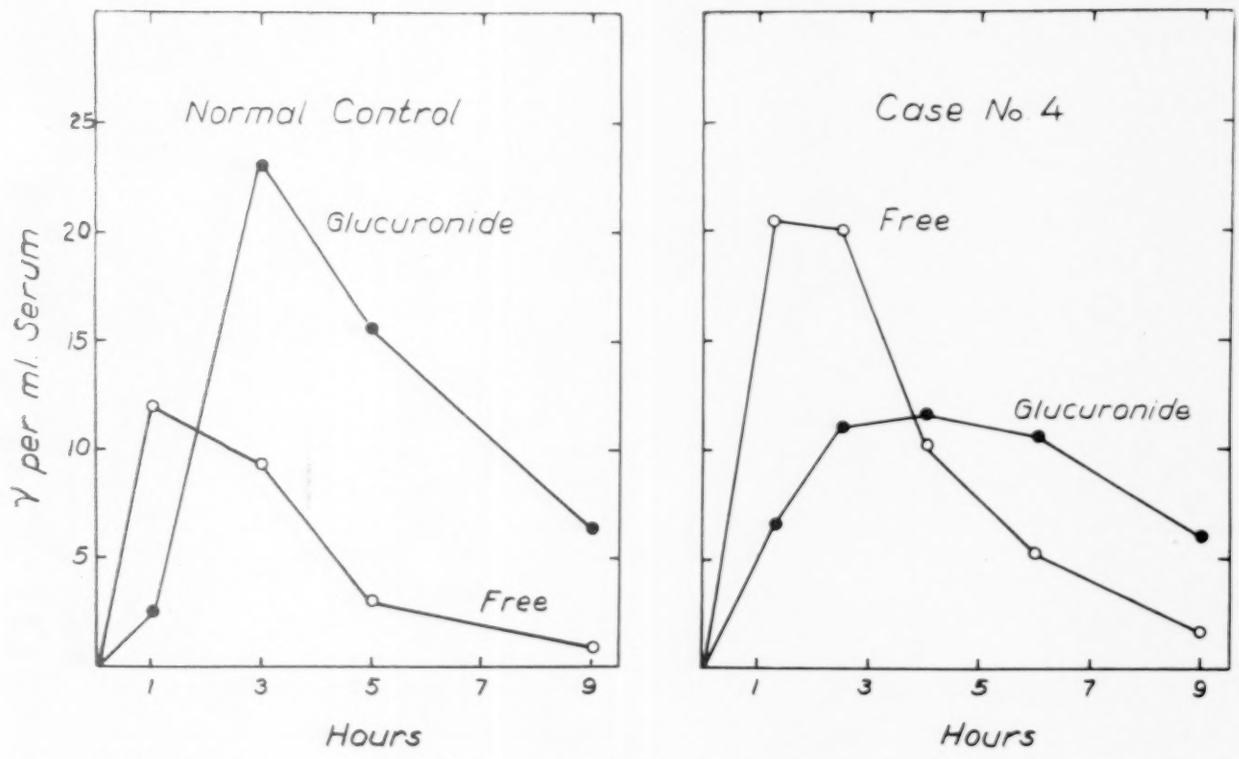


FIG. 1. Serum levels of free p-hydroxyacetanilide and its glucuronide following a single oral dose af 24 mg. p-hydroxyacetanilide per kg. body weight.

Whatman No. 3MM paper strips suspended in barbital buffer, pH 8.6 and ionic strength 0.025. After nine hours of electrophoresis at 400 volts and 0.3 ma. per cm. width of paper, no difference in migration rates could be observed between normal adult and test samples.

Absorption spectrums of hemoglobin solutions: The absorption spectrums of the oxyhemoglobin, methemoglobin, carboxyhemoglobin and hemochromogen derivatives were identical with patterns obtained for normal blood.

Dimethyl ester of protoporphyrin IX: To establish the structure of the porphyrin ring it was decided to prepare the dimethyl ester of protoporphyrin and to determine its melting point, its absorption and emission spectrums, as well as chromatographic behavior. The protoporphyrin dimethyl esters were prepared by the procedure of Grinstein [7], applied to test samples of blood and to normal adult blood. The melting points of the recrystallized products were as follows: normal adult (control), 214° to 217°C.; Case I, 214° to 216°C.; Case II, 213.5° to 216.5°C.; Case III, 215° to 217°C.; normal values cited [8], 214° to 217°C.

Traces of the dimethyl esters were dissolved in chloroform and the absorption spectrums of the resulting solutions were determined in the Beckman DU spectrophotometer. The absorption spectrums in the visible range showed peaks at 507, 542, 575 and 631 mμ. These absorption maximums were the same as those determined for the control specimens.

The fluorescence spectrums of the dimethyl esters of protoporphyrin were determined on small amounts of the crystalline esters dissolved in dioxan to give a final concentration in the order of 1 in 50,000. Intensity of fluorescence of these solutions at various wavelengths when radiated with ultraviolet light was measured by means of a photoelectric cell connected to a scaler. There was no difference in the emission spectrums of the test samples as compared with the control samples.

Paper chromatography of the protoporphyrin dimethyl esters by the method of Chu, Green and Chu [9] was performed. No significant difference was noted in the patterns obtained for normal and test samples.

Absorption spectrums of serum bilirubin: Bilirubin was prepared from serum by the method of Cole and Lathe [10] and subsequently taken up in chloroform. The absorption spectrums in the ultraviolet and visual ranges were identical in the test samples and in the control.

Serum Lactic Dehydrogenase. This was determined according to the method of Blanchaer et al. [11]. The normal range is 5 to 13 units. The values obtained in Cases I to IV were 10, 13, 8.7 and 7 units respectively.

TABLE I

Data	Case I (Trudy P)		Case II (Anton P)		Case III (Herman P)	Father (Mr. P)	Mother (Mrs. P)	Case IV (Mrs. W)	
	Before Splenectomy	After Splenectomy	Before Splenectomy	After Splenectomy				Before Splenectomy	After Splenectomy
Red blood cells (millions per cu. mm.)	4.2	4.2–4.35	4.1–4.7	5.0	5.4–5.8	5.33	5.02	3.6	4.1–4.3
Hemoglobin (gm. per 100 ml.)	12.5	12.8–13.9	12.1–14.5	14.3	15.4–16.1	14.3	14.9	10.3	11.3–12.6
Hematocrit (%)	35	36–39	37–39	44	47–49	45	44	.....	35
Mean corpuscular volume (cu. μ)	85	87	84	90	80	85	88	.....	83
Mean corpuscular hemoglobin (μμg.)	30	30	30	30	28	27	29	.....	27
Mean corpuscular hemoglobin concentration (%)	36	36	35	35	34	31	34	.....	32
Spherocytes	+	++	+	++	+	−	−	+	++
Reticulocytes (%)	4.0–5.1	1.2–4.4	2.0–4.6	2.0	1.1–3.3	2.3	1.6	3.2–4.0	2.0–4.1
Serum bilirubin (mg. %) Total	8.5	2.4–3.4	4.6–7.8	2.2–3.2	2.13	.70	.55	4.8	2.7
Indirect	7.5	2.0–3.0	4.1–6.9	1.6–2.7	2.0	.70	.55	4.2	2.0
Osmotic fragility (% saline) Not incubated	.55–.35	.65–.35	.55–.25	.....	.55–.35	.50–.20	.50–.30	.....	.60–.30
Incubated	.76–.30	.80–.40	.80–.25	.....	.80–.40	.70–.30	.70–.30	.....	.80–.40
Autohemolysis (48 hours)	.....	1.8	4	.....	3.6	2.6	2.7	.....	4.0
Mechanical fragility (%)	.....	4.2	1.7	.....	1.7	1.5	1.0	.....	3.1
Coombs' test (direct and indirect)	Negative	Negative	Negative	.....	Negative	.....	.....	Negative	Negative
Bone marrow (% normoblasts)	76	.....	71	.....	36	.....	.....	.....	60
Cr^{51} red cell survival (T/2)	.....	28	19	34	26	.....	.....	.....	28
Serum iron (μg. per 100 ml.)	.....	85	.....	190	121	95	116	.....	87
Urine urobilinogen (mg. per 24 hours)	40	20–24	25	15	2.4	0.53	1.0	.....	38
Fecal urobilinogen (mg. per 24 hours)	.....	576	.....	963	252	140	98	.....	840
Bilirubin tolerance test (% retention at 3 hours)	.....	24	0	0	25	12	8	.....	30
Formation of glucoronide of p-hydroxy-acetanilide	.....	.....	.....	Normal	Normal	.....	.....	.....	Slow
Bromsulphalein (% retention in 45 minutes)	0	.....	0	.....	0	.....	.....	.....	0

CASE REPORTS

Family P

CASE I. Trudy is twenty-three years old. Her blood groups are O, CDe/CDe, MN, S+, P+, K− and Fy(a)+. When she was first seen Trudy was twenty years old. She had been well until the age of twelve when she noted for the first time that her skin and sclerae were icteric. Her parents noted that the jaundice fluctuated in degree. There was no episode suggestive of infectious hepatitis. She had always felt well but was self-conscious of the profound icterus.

When she was first seen in 1955, she was observed over a period of four weeks. Physical examination at that time revealed only marked jaundice. The spleen was palpable at the left costal margin; the liver was not palpable. The hematologic findings are shown in Table I. Spherocytes were present in the peripheral blood. The reticulocyte count ranged from 4.0 to 5.1 per cent. The serum bilirubin was 8.5 mg. total with 7.5 mg. indirect reacting pigment. No hemosiderin was present in the urine. A bone marrow examination showed marked hyperactivity of the erythroid series at the normoblastic level. It is to be noted that the serum bilirubin was much higher than one would have expected in uncomplicated hemolysis in the absence of any appreciable anemia and with a reticulocyte count of 4 to 5 per cent.

A splenectomy was performed in October 1955. The spleen weighed 340 gm. Histologically, the pulp and sinuses contained an increased amount of blood. The endothelial lining of the sinusoids was prominent. There was no evidence of extramedullary blood formation. Hemosiderin was absent.

The findings after splenectomy are shown in Table I. There was a slight increase in hemoglobin amounting to somewhat more than 1 gm. per 100 ml., and the reticulocyte count decreased to 1.2 to 4.4 per cent. The total serum bilirubin fell to 2.4 to 3.4 mg. per cent. The spherocytes in the peripheral blood increased in number and the osmotic fragility remained essentially unchanged. Following splenectomy the Cr^{51} red cell survival half-life was twenty-eight days. A bilirubin tolerance test showed 24 per cent retention of bilirubin at the end of three hours. The urinary urobilinogen excretion was 20 to 24 mg. in twenty-four hours. The fecal urobilinogen was 600 mg. in twenty-four hours in a four day stool collection (260 mg. per 100 gm. of wet stool). Results of the thymol turbidity, thymol flocculation and cephalin-cholesterol flocculation tests were negative. The alkaline phosphatase was 5.9 units (King-Armstrong). Bromsulphalein retention was zero in forty-five minutes.

CASE II. Anton is sixteen years old. His blood groups are B, CDe/CDe, MN, S−, P+, K− and Fy(a)+. Anton, the brother of Trudy, is the youngest member of the family. His parents had predicted correctly that he would probably become jaundiced at the age of puberty, following the same pattern as his brother and sister. He was a healthy child but for the appearance of icterus at the age of thirteen. This icterus was noted to fluctuate in intensity and it was thought to be more marked at times when he was

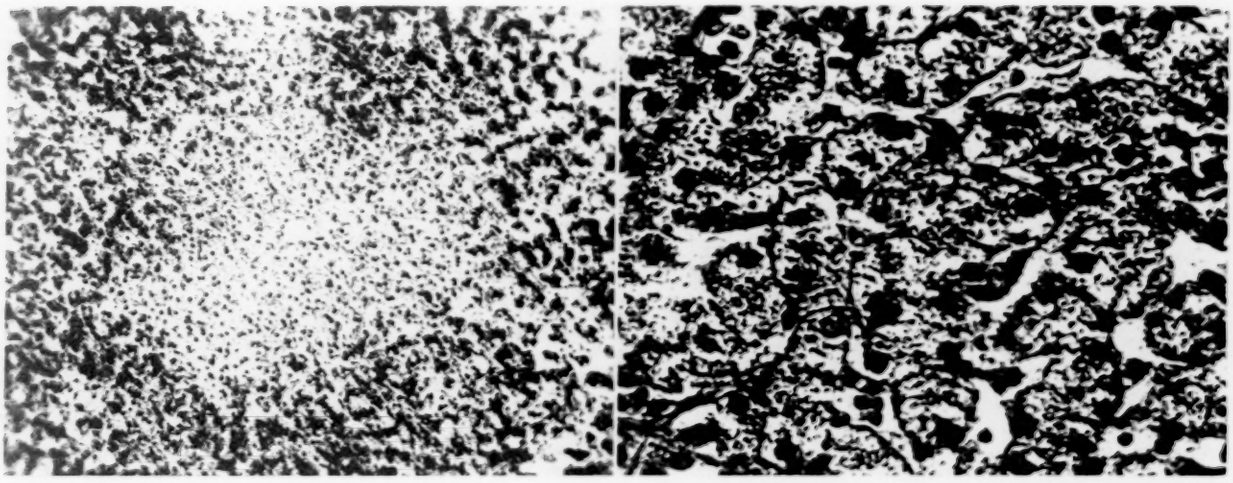


FIG. 2. Case II. Photomicrographs of the liver biopsy specimen. *Left*, Prussian blue stain showing intense deposition of hemosiderin in the parenchymal cells in the periphery of the lobule. Original magnification × 100. *Right*, hematoxylin and eosin stain showing the granules in the hepatic cells. Original magnification × 500.

feeling tired or unwell. There was no history of infectious hepatitis.

On physical examination he was a well nourished, intelligent young boy. There was marked icterus of the skin and sclerae. The spleen was palpable 1.5 cm. below the left costal margin; the liver was not palpable. The hematologic findings are shown in Table I. Anton was observed for six months prior to splenectomy during which time his erythrocyte count varied from 4.1 to 4.6 million per cu. mm. and his hemoglobin from 12.1 to 14.5 gm. per 100 ml. The reticulocyte count ranged from 2 to 4.6 per cent. The serum bilirubin was high, the total ranging from 4.6 to 7.8 mg. per cent of which most of the pigment was indirect reacting. Numerous spherocytes were present in the peripheral blood. The marrow was very cellular, with marked normoblastic hyperplasia. The Cr^{51} red cell survival T/2 was nineteen days. No hemosiderin was present in the urine. There was 25 mg. of urobilinogen in the urine in twenty-four hours. A bilirubin tolerance test showed complete clearance of 50 mg. of injected bilirubin at three hours. Results of the thymol turbidity and thymol flocculation tests were negative; cephalin-cholesterol flocculation was 2 plus; and alkaline phosphatase 6 King-Armstrong units. The bromsulphalein test showed no dye retention at forty-five minutes.

A splenectomy was performed in December 1957. The spleen weighed 350 gm. and histologically the pulp and sinuses contained prominent endothelial cells. An iron stain revealed only a small amount of hemosiderin. A biopsy specimen of the liver taken at the same time showed the liver parenchymal cells to be normal but to contain large numbers of brown granules in the periphery of the lobule. These granules gave a strongly positive Prussian blue reaction for iron. (Fig. 2.)

The postoperative hematologic findings are shown in Table I. There was little change in the red cell series but for a drop in the number of reticulocytes to 2 per cent; the total serum bilirubin now ranged from 2.2 to 3.2 mg. per cent. The Cr^{51} red cell survival T/2 was now thirty-four days. A repeat bilirubin tolerance test again showed no retention at three hours. The urinary urobilinogen excretion was 15 mg. in twenty-four hours and there was 963 mg. of urobilinogen in the stool in twenty-four hours as calculated from a four day stool collection (670 mg. per 100 gm. of wet stool).

CASE III. Herman is twenty-six years old. His blood groups are B, CDe/CDe, MN, S−, P−, K− and Fy(a)+. Herman is the brother of Trudy and Anton; he too had no significant childhood illnesses. At the age of puberty his parents had noticed the onset of a mild degree of icterus.

On physical examination he was mildly icteric; the spleen was palpable at the costal margin. There were no other positive physical findings. The hematologic findings are shown in Table I. Herman has never been noted to be anemic. The reticulocytes have ranged from 1.1 to 3.3 per cent. An occasional spherocyte was seen in the peripheral blood. The osmotic fragility was within the normal range in the unincubated specimen but showed markedly increased hemolysis on incubation. The bone marrow showed normoblastic hyperplasia of mild degree with 36 per cent normoblasts. The Cr^{51} red cell survival T/2 was twenty-six days. The urine urobilinogen excretion was 2.5 mg. in twenty-four hours, and the fecal urobilinogen 250 mg. in twenty-four hours in a four day stool collection (135 mg. per 100 gm. wet stool). The bilirubin tolerance test showed 25 per cent retention at three hours. The thymol turbidity, thymol flocculation and cephalin-cholesterol flocculation tests were all within normal limits. The alkaline phosphatase

was 6 King-Armstrong units. There was no bromsulphalein retained at the end of forty-five minutes.

Father. Mr. P. is fifty-five years old. His blood groups are O, CDe/cDE, NN, S−, P+, K− and Fy(a)+. He is the father of the three children described. His health had always been good although there was a short episode of jaundice at the age of twelve.

Physical examination revealed no abnormalities; there was no icterus or hepatosplenomegaly. Neither his parents nor any of his brothers or sisters had been jaundiced. The laboratory findings in Mr. P. are shown in Table I and fall within normal limits but for a slight elevation in the reticulocyte count. The fecal and urinary urobilinogens were normal and he was able to excrete 88 per cent of an intravenous dose of 50 mg. of bilirubin within three hours.

Mother. Mrs. P. is fifty-three years old. Her blood groups are B, CDe/CDe, MM, S−, P−, K− and Fy(a)+. She is the mother of the three children described. Mrs. P. is a hard-working woman whose health had always been good. There was no history of jaundice. Physical examination was completely normal. She comes from a large family; her parents were not known to have been jaundiced, nor were any of her brothers or sisters. The laboratory findings are as indicated in Table I, and all are within normal limits. Both Mr. and Mrs. P. are of Mennonite extraction.

Family W

CASE IV. Mrs. W. is forty years old. Her blood groups are O, CDe/CDe, MN, S+, K−, Fy(a)+ and Le(a)+. Mrs. W. lives in a village 5 miles from the P. family. No direct relationship between the two families is known. This Mennonite woman was asymptomatic until the age of eighteen when she was found to be jaundiced. She was seen at that time by a physician who noted that she was also anemic. Her health was good except for jaundice and easy fatiguability. She married at the age of twenty-one. At age thirty-one, splenomegaly was noted for the first time. One year later she was admitted to the hospital for investigation. At that time physical examination revealed a mild degree of icterus and a spleen which was palpable 2 cm. below the left costal margin. The laboratory findings are shown in Table I. A diagnosis of congenital spherocytic anemia was made and a splenectomy was performed in July 1954. The spleen measured 14 by 9 by 8 cm. and weighed 300 gm. Microscopic examination showed the spleen to be congested and the endothelial cells lining the sinuses were prominent. There was no excess deposition of iron. Following splenectomy the hemoglobin rose, the serum bilirubin fell and the jaundice was less marked; the patient still tired easily but was otherwise well.

At the present time, physical examination is not remarkable except for minimal scleral icterus. The present findings in the peripheral blood are shown in Table I. The hemoglobin now ranges from 11.3 to 12.6 gm. per 100 ml. and the red count from 4.1 to 4.3 million per cu. mm. The reticulocytes on repeated examination have ranged from 2 to 4.1 per cent. The Cr^{51} red cell survival T/2 was twenty-eight days. The urobilinogen excretion in urine was 38 mg. in twenty-four hours; in the stool, 840 mg. in twenty-four hours. Cephalin flocculation was 2 plus; thymol turbidity, 2 units; thymol flocculation, negative; prothrombin time, 12.4 seconds (100 per cent); alkaline phosphatase, 8.0 King-Armstrong units; bromsulphalein, no retention of dye in forty-five minutes. A bone marrow examination showed a cellular marrow with marked normoblastic hyperplasia, the normoblasts forming 60 per cent of the total nucleated count. The bilirubin tolerance test revealed 30 per cent bilirubin retention at the end of three hours. A biopsy specimen of the liver showed normal parenchymal cells with a heavy deposition of iron-positive brown granules in the periportal areas. The Kupffer cells were numerous and loaded with the same iron-positive pigment.

The family history was non-contributory. Her parents, siblings and children have never been jaundiced. Physical examination, peripheral blood findings and urobilinogen excretions of her three sons, aged sixteen, twelve and six years, were all within normal limits. However, Mrs. W. did not become jaundiced until the age of eighteen.

COMMENTS

All the affected subjects described noted the onset of jaundice during the second decade of life. In no case was there a history of antecedent hepatitis. All had many of the features of congenital spherocytosis such as jaundice, splenomegaly, spherocytes in the peripheral blood, and an increased osmotic fragility on incubation. The marrow showed normoblastic hyperplasia and there was a reticulocytosis of 2 to 5 per cent. The urobilinogen excretion was high. The Cr^{51} survival before splenectomy in the one subject in which it was measured was short.

There are, however, some notable differences from congenital spherocytosis. Autohemolysis and mechanical fragility were normal. Although splenectomy extended the Cr^{51} survival time to normal and reduced the serum bilirubin and the urine urobilinogen to about one-half of the preoperative level, an appreciable hyperbilirubinemia persisted. The reticulocytosis persisted, although to lesser degree, and the marrow remained normoblastic. The total urobilinogen output remained high (up to 978 mg. per twenty-four hours) in the presence of a normal Cr^{51} red

cell survival time. It should be noted that in all subjects the hyperbilirubinemia was far in excess of what one would expect from the hemoglobin level and reticulocyte count.

No abnormalities in the standard liver function tests were found. Serum flocculation tests, alkaline phosphatase, and bromsulphalein excretion were normal. The bilirubin tolerance test showed no retention of pigment in three hours in one patient (Case II), while three patients (Cases I, III and IV) retained 24, 29 and 30 per cent of the bilirubin three hours after a 50 mg. injection. Eilbott [*3*] and Von Bergmann [*4*] considered any retention in excess of 15 per cent at three hours as pathologic; so that some defect in bilirubin clearance may be present in three of the subjects. Kalk, however, has taken 30 per cent bilirubin retention at three hours as the pathologic level [*12,13*]. The youngest patient studied (Case II) could clear the injected bilirubin at a rapid rate. Perhaps he, too, will in time acquire this defect. Two patients (Cases II and III) conjugated p-hydroxyacetanilide with glucuronic acid at a normal rate but one (Case IV) showed a reduced rate of glucuronide formation. This moderate impairment of glucuronide formation and bilirubin clearance may be contributory to the hyperbilirubinemia in Case IV.

Splenomegaly was present in all patients. The histology was not remarkable and there was little deposition of iron pigment. The biopsy specimen of liver obtained in two subjects was of great interest. In both there was a heavy infiltration of brown pigment occurring as granules of irregular shape and size in the hepatic parenchymal cells. This pigment was concentrated primarily in the peripheral areas. The Kupffer cells were numerous and most were filled with this pigment. The Prussian blue stains showed almost all the pigment to be iron and were strikingly positive in the peripheral areas of the lobule. (Fig. 2.) A small amount of the pigment in the centrilobular areas did not take on the Prussian blue stain. This is in contrast to the usual findings in the liver in congenital spherocytic jaundice in which the histology is apt to be normal or at most shows only moderate iron deposition in the Kupffer cells [*14*].

The overproduction of bilirubin in the presence of a normal red cell survival together with borderline bilirubin clearance rate in Cases I, III and IV suggested the possibility of an abnormality in the tetrapyrrole component of the hemoglobin (an abnormal heme). It was postulated that this might render the erythrocyte susceptible to premature destruction in the peripheral blood and in the marrow, and might give rise to an abnormal bilirubin which could be excreted only with difficulty. No experimental evidence was obtained to support this concept.

The hyperbilirubinemia in the cases described is apparently due to overproduction in the absence of significant hemolysis (postsplenectomy). Whipple [*15*] conceived the idea of a pigment pool from which pigment, such as bilirubin or urobilin, might be produced from sources other than the hemoglobin molecule. Watson and Jones [*16*] observed that in pernicious anemia in relapse the hemoglobin level remained stable despite a markedly increased urobilinogen excretion and a low absolute reticulocyte count. They concluded that a major part of the fecal urobilinogen was coming from sources other than the hemoglobin of circulating red cells. Castle and Minot [*17*] also suggested that in pernicious anemia there is faulty utilization of pigment associated with maturation arrest in the bone marrow, with resulting accumulation and excess excretion. Jedlicka [*18*] suggested that the excess of pigment excretion in pernicious anemia might be due to the manufacture and destruction of unused hemoglobin in the bone marrow. Kalk [*12,13*] postulated that in his cases of posthepatitic hyperbilirubinemia the bilirubin was derived not from hemoglobin but directly from protoporphyrin IX.

London and his associates [*19*], using N^{15}-labelled glycine both orally and intravenously, were able to recover about 11 per cent of the labelled glycine in the stercobilin excreted during the eight-day period following its administration. This 11 per cent which was excreted early in the course of the experiment suggested that the source of the stercobilin was not the mature circulating erythrocyte. It was suggested that the bile pigment was formed from the hemoglobin of erythrocytes which were destroyed in the bone marrow before reaching the peripheral blood or from the hemoglobin of newly formed erythrocytes which were destroyed shortly after entering the circulation. Another possibility suggested was that of the intracorpuscular degradation of hemoglobin and formation of bile pigment which might occur in the developing erythrocytes in the bone marrow prior to their release into the peripheral blood. It was also

considered that the bile pigments might have been derived from heme or porphyrins which were not utilized for hemoglobin production. Further studies using N^{15} glycine indicated that in pernicious anemia and congenital porphyria, 30 to 40 per cent of the stercobilin was not derived from the hemoglobin of the circulating erythrocyte [*20,21*]. In the case of congenital porphyria studied by London and his co-workers the patient had a normoblastic hypercellular marrow and a reticulocytosis in the presence of a normal red cell survival. These findings are analogous to those in Cases I to IV.

In the cases described herein the total urobilinogen excretion was as high as 978 mg. in twenty-four hours (Case II). Since the red cell survival was within normal limits, this 70 kilo boy derived approximately 240 mg. of bilirubin from the hemoglobin of circulating erythrocytes in twenty-four hours [*22*]. If there was no loss of pigment then this would appear as a maximum of approximately 240 mg. of urobilinogen in urine and stool. Thus in Case II no less than 75 per cent of the total pigment excreted was derived from sources other than the hemoglobin of circulating erythrocytes. The reticulocytosis and normoblastic marrow in the absence of peripheral erythrocyte destruction suggest the marrow erythrocytes, or their precursors, to be the source of the excess pigment.

We consider the probable mechanism responsible for this overproduction of hyperbilirubinemia to reside within the red cell or its precursors. In our cases, the mature cells were spherocytic and susceptible to early destruction in the spleen. This source of hyperbilirubinemia was removed by splenectomy. Increased production of bilirubin and urobilinogen continued, however, having as its source either hemoglobin derived from destruction of non-circulating erythrocytes or normoblasts, or the heme or tetrapyrrole precursors of hemoglobin. The hypercellular normoblastic marrow and reticulocytosis in the presence of a normal peripheral red cell survival time suggest this to be the site of pigment formation.

The serum lactic dehydrogenase activity has been noted to be increased in frank hemolysis [*23*], but not in the anemia of acute and chronic blood loss [*24*]. This suggests that cell destruction, rather than increased erythropoietic cellular activity, is responsible for the increase in enzyme activity. It has also been noted that the enzyme activity is high in megaloblastic anemia in relapse, and falls when adequate therapy corrects the deficiency. One might surmise that here, too, cell destruction was taking place —largely in the marrow as postulated by Jedlicka. The normal lactic acid dehydrogenase in our cases suggests that the excess pigment may come directly from cellular synthesis rather than from marrow erythrocyte destruction. We have termed this hyperbilirubinemia due to a short-cut in bilirubin production as "shunt" hyperbilirubinemia because the excess bilirubin is not derived from the hemoglobin of the circulating erythrocytes.

The different mechanisms leading to an increased level of indirect reacting bilirubin in shunt hyperbilirubinemia, hemolytic anemia, and congential non-hemolytic hyperbilirubinemia are shown in Figure 3. The differentiation from congential spherocytic anemia has already been discussed. Congenital non-hemolytic hyperbilirubinemia is easily distinguished from shunt hyperbilirubinemia. In congenital non-hemolytic hyperbilirubinemia there is no splenomegaly; the urobilinogen excretion is normal; there is no reticulocytosis or normoblastic hyperplasia of the marrow. There is a marked inability to excrete injected bilirubin due to a defect in the glucuronide conjugation mechanism. This is also reflected in the inability to form the glucuronide of p-hydroxyacetanilide [*5*].

Our patients resemble most some of the cases reported by Kalk [*12,13*] and Siede [*25*]. Kalk investigated one hundred and sixty-five cases in which a syndrome characterized by hepatomegaly, splenomegaly and elevated indirect serum bilirubin followed epidemic hepatitis by a period of months or years. In 37 per cent there was a diminished bromsulphalein clearance and in 67 per cent the bilirubin tolerance test was abnormal (more than 30 per cent bilirubin retention in three hours). A reticulocytosis was present in 37 per cent and the osmotic fragility was increased in 37 per cent. No spherocytes were seen in the peripheral blood. The bone marrow was hyperactive at a normoblastic level. The excretion of urobilinogen in some cases was increased. Liver biopsy specimens showed no cellular pathologic condition except for the presence of brown granules in the parenchymal cells which did not take the stain for iron.

The cases Kalk reported following hepatitis are of great interest. We have also observed one such case and it would seem that here, too, a

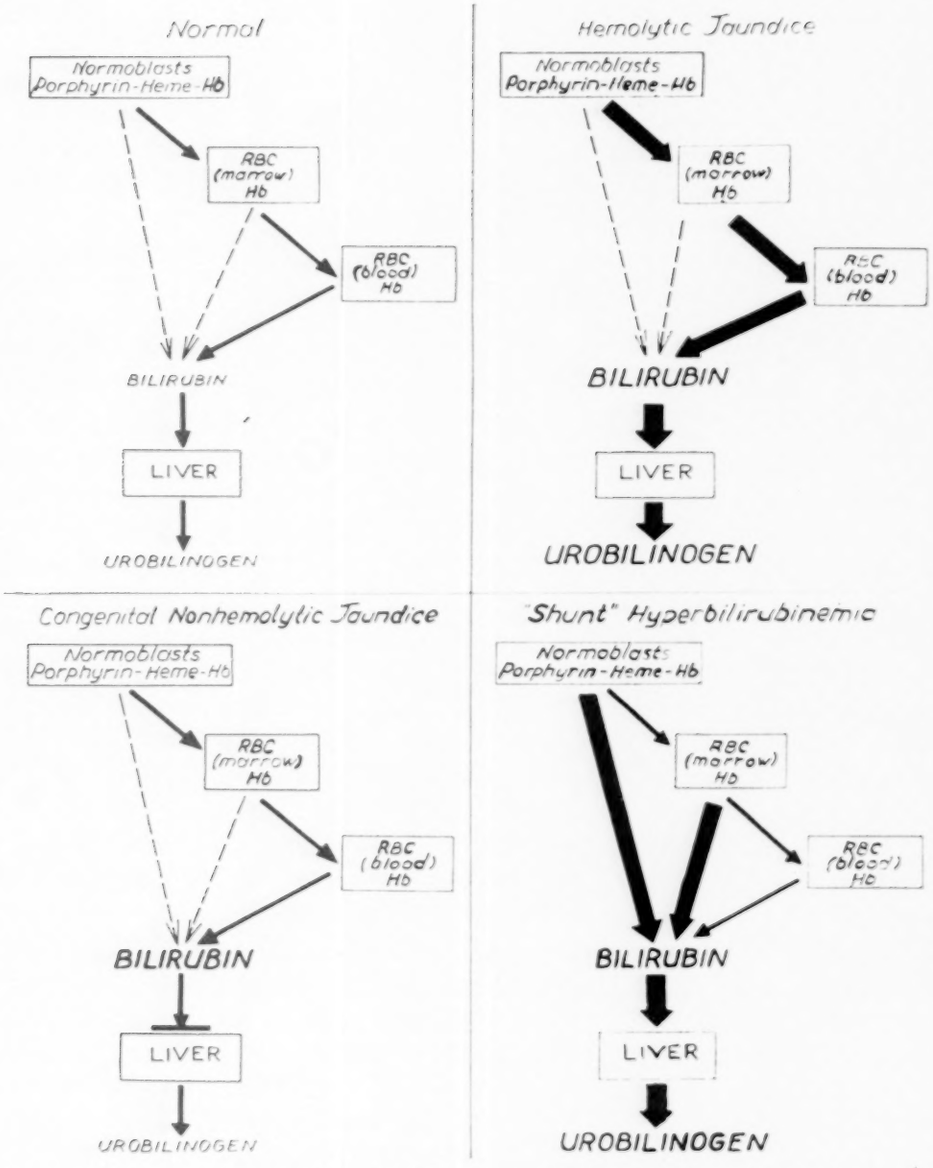


FIG. 3. A schematic representation of the pathways of bilirubin and urobilinogen formation in the normal subject, and in subjects with hemolytic jaundice, congenital nonhemolytic jaundice and shunt hyperbilirubinemia. In the latter, the excess bilirubin production is thought to take place in the marrow and has as its source the marrow erythrocytes or their precursors. The alternate pathways indicate that this source may be either the hemoglobin of destroyed cells or the synthesis by these cells or their precursors of bilirubin directly from heme or heme precursors.

shunt mechanism was responsible for the hyperbilirubinemia and increased urobilinogen excretion. This was a twenty-six year old Canadian veteran who was exposed to epidemic hepatitis while working as an orderly in a hospital in Korea. He was well but for the incidental findings while in the hospital of a serum bilirubin of 2.5 mg. of which 2.0 mg. was indirect reacting pigment. The urobilinogen excretion in the urine was 16 mg. in twenty-four hours and 415 mg. in twenty-four hours in the stool. Bilirubin tolerance showed 50 per cent retention in three hours. He retained 22 per cent of the injected dose of bromsulphalein in thirty minutes. There were no spherocytes in the peripheral blood. The osmotic fragility was normal. The

reticulocyte count varied between 1 and 3 per cent. A biopsy specimen of the liver showed no abnormalities except for a small amount of round cell infiltration in the portal tracts. There was no stainable iron in the liver parenchymal cells.

Siede [*25*] has described a non-hemolytic hyperbilirubinemia, some cases of which followed epidemic hepatitis. Some patients had hepatomegaly and splenomegaly; there was an increased indirect reacting serum bilirubin and a markedly increased urobilinogen excretion. The bilirubin tolerance test showed diminished capacity to excrete bilirubin and there was diminished capacity to excrete bromsulphalein. Spherocytosis, reticulocytosis and increased erythrocyte osmotic fragility were not observed. The biopsy specimen of the liver showed normal hepatic architecture with deposition of brown granules in the parenchymal cells.

The four cases presented in this paper belong to one ethnic group. The appearance of three cases in one family strongly suggests that this is a familial disease. Not enough data are available to assess accurately its mode of transmission but it would seem to be an autosomal recessive characteristic. The Mennonites of Manitoba are mainly of Dutch origin. The term Mennonite refers, in a strict sense, to members of a Protestant denomination which takes its name from Menno Simons but it is used also in an ethnic sense to denote descendants of Mennonites who came, in the main, from two national groups, the Dutch and the Swiss. Shortly after 1530, large groups of Mennonites left the Netherlands to settle in northwestern Germany. Crefeld became one of the most important centers of Mennonite life in Germany and has remained so to this day. Other emigrations from the Netherlands to the Hamburg and Danzig areas followed. More than 200 years later, in 1789, descendants of these Mennonites emigrated to Russia. During the years 1874 to 1880, eight thousand left Russia for new homes in Manitoba. Further waves of emigration from Russia followed the Russian revolution and many of the 21,000 migrants came to Canada. As a rule, Mennonites have migrated in large groups forming compact, primarily agricultural settlements and have developed into well integrated ethnic communities. It is interesting, therefore, to speculate that some of the patients seen by Kalk in Kassel which is near Crefeld may have the same racial background, and quite possibly the same disease, as our four patients (Cases I to IV).

It is possible that overproduction or shunt hyperbilirubinemia may not be an uncommon mechanism in the production or potentiation of jaundice. We have presented evidence for its occurrence in four patients with spherocytosis. We think the same mechanism is sometimes seen or unmasked in liver disease, as evidenced by our one case and the extensive reports of Kalk and Siede. It may also be operative in untreated megaloblastic anemia. The mechanism may be analogous to that in congenital porphyria in which the marrow is the source of the excess porphyrin production. In shunt hyperbilirubinemia it may be the source of excess bilirubin synthesis. The occurrence of hyperbilirubinemia due to a primary overproduction of bilirubin as described must then be added to the possible causes of jaundice.

SUMMARY

Four cases of jaundice are described in which the hyperbilirubinemia was not related to the breakdown of circulating erythrocytes or to a defect in hepatic function. Three of the cases described occurred in one family and are thought to represent a congenital abnormality of excessive bilirubin production from sources other than the circulating red cell. This primary overproduction of bilirubin has been termed "shunt" hyperbilirubinemia.

The hyperbilirubinemia was characterized by the onset of jaundice and splenomegaly in early adult life. The serum bilirubin was predominantly indirect reacting pigment, and the red cell survival somewhat short prior to splenectomy. The urobilinogen excretion in urine and stool was high. Hemolysis, when present, was corrected by splenectomy but the reticulocytosis, normoblastic hyperplasia of the marrow, hyperbilirubinemia and increased urobilinogen excretion persisted. The liver showed gross hemosiderin deposits in the parenchymal cells in the periphery of the lobule. It is suggested that the excess bilirubin has as its source the marrow erythrocytes or their precursors, either by their destruction or their synthesis of bilirubin directly from heme or its tetrapyrrole antecedents.

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A Survey for Hemagglutinins in Viral Hepatitis*

ROBERT W. MCCOLLUM, M.D., VIGGO BECH, M.D.,† PETER ISACSON, M.D. *and* JOHN T. RIORDAN

New Haven, Connecticut

To date there have been no independently confirmed reports of isolation of an etiologic agent or agents of human viral hepatitis by inoculation of laboratory animals or tissue cultures. For this and other obvious reasons a specific immunologic test for the diagnosis of either infectious or serum hepatitis or both would be of major importance in clinical and epidemiologic studies. A number of reactions occurring in the serums of patients with infectious or serum hepatitis have been described in the past, but the usefulness of the procedures has been limited by the apparent lack of specificity. A review of this literature up to 1954 has been given by Havens [*1*].

Within the past few years a number of attempts have been made to utilize the agglutination of monkey and chick erythrocytes as a serologic test in viral hepatitis. Hoyt and Morrison [*2*], using rhesus monkey erythrocytes, reported positive hemagglutination reactions (serum titer of 1:8 or higher) in 74 per cent of serums from cases of viral hepatitis. Rubin et al: [*3*], using the same type of erythrocytes, also found elevated titers in viral hepatitis serums and suggested that these high titers might be due to a specific effect of the hepatitis virus. Certain differences between the serums of infectious and serum hepatitis were also noted.

Morris [*4,5*] has described a chick erythrocyte agglutination test for hepatitis based on acetone and ether extraction of the serums in order to remove non-specific agglutinins and inhibitors. His results suggested that the agglutinins found in hepatitis serums are of more than one type, but that they are present in a large majority of such serums and that their titers reflect to some degree the course of the illness. Serums from control patients, including other infectious diseases, gave negative results with few exceptions. Using a similar method of extraction but a different buffer system, Havens [*6*] reported agglutination of chick erythrocytes in over 70 per cent of serums from patients in the acute phase of viral hepatitis. Seven per cent of normal persons, 13 per cent of patients with chronic hepatic disease and 17 per cent of patients with other acute and chronic diseases gave positive results. No chick erythrocyte agglutinins were found in serums from patients with obstructive jaundice.

The present report is concerned with attempts to confirm the findings of rhesus monkey and chick erythrocyte agglutinins in serums from patients with viral hepatitis, and to test further the specificity of these reactions by the examination of serums from normal persons and from patients with a wide spectrum of clinical disorders.

MATERIALS AND METHODS

Serums. Serums from patients with hepatitis, patients with other infectious and non-infectious diseases, and normal control subjects were obtained from a variety of sources. Besides collections of serums from patients in the Yale Medical Center, many of the hepatitis serums were obtained from patients in U. S. Military Hospitals in Germany.* Some serums were tested within a few days after collection. Others were stored at −20°c. for periods ranging from one week to six years.

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* From the Section of Epidemiology and Preventive Medicine, Yale University School of Medicine, New Haven, Connecticut. This work was done under the sponsorship of the Commission on Viral Infections of the Armed Forces Epidemiological Board and was supported by the Office of the Surgeon General, Department of the Army.

† Visiting scientist at Yale University from April 1957 to August 1958. Present address: State Serum Institute, Copenhagen, Denmark.

TABLE I

RHESUS ERYTHROCYTE AGGLUTININ TITERS OF FIFTY-ONE SERUMS FROM PATIENTS WITH HEPATITIS, AND OTHER PATIENTS AND NORMAL CONTROLS

Serum Group	Reciprocals of Serum Hemagglutinin Titers							No. Positive* / No. Tested	Per cent Positive
	<2	2	4	8	16	32	64		
Viral hepatitis	..	2	8	7	2	1	2	12/22	54.5
Obstructive jaundice	..	5	3	..	..	..	..	0/8	0.0
Acute infections	1	..	5	..	1	..	..	1/7	14.3
Normal	4	1	2	3	1	1	2	7/14	50.0

* Serum titer of 1:8 or greater considered positive.

TABLE II

VARIOUS HEMAGGLUTININ TITERS OF TWENTY SERUMS* BEFORE AND AFTER ONE ABSORPTION WITH SHEEP ERYTHROCYTES

Cells Used in Hemagglutination Tests	Reciprocals of Hemagglutinin Titers													
	No. of Unabsorbed Serums with Titer of:							No. of Absorbed Serums with Titer of:						
	<8	8	16	32	64	128	>128	<8	8	16	32	64	128	>128
Rhesus monkey	..	10	4	2	4	..	..	20	..	..	..	..	..	..
Sheep	..	1	1	14	3	..	1	19	..	..	..	..	1	..
Day old chick	5	5	6	2	2	..	..	7	8	3	2	..	..	..

* Serums from control subjects and patients with hepatitis rated positive by the Hoyt-Morrison test.

Agglutination Technics. In all hemagglutination tests special attention was paid to the care of glassware. Since Bang [7] has demonstrated that a trace of soap can produce a false positive result, acid-cleaned glassware was used exclusively.

Rhesus Monkey Erythrocytes. Fifty-one serums were tested according to the method of Hoyt and Morrison [2] and by modifications of this method involving preabsorption of the human serums to be tested with sheep erythrocytes (obtained from a commercial source), and comparison of chick cell agglutinins with rhesus cell agglutinins in absorbed and unabsorbed serums. Rhesus monkey erythrocytes, obtained from our own Macaca mulatta monkey colony, were collected and stored in Alsever's solution and washed three times in physiological saline solution prior to use. They were not used when more than three days old. Serum absorption was carried out by mixing serum with an equal volume of a 25 per cent sheep erythrocyte suspension in saline solution and incubation overnight at 4°c. After centrifugation the supernate was used as the 1:2 serum dilution for testing. A titer of 1:8 was considered positive. Chick erythrocytes obtained from one day old chicks were washed in saline solution three times and stored from one to four days as a 10 per cent suspension in Alsever's solution. Prior to use they were again washed and resuspended as 2 per cent cells in physiological saline solution.

Chick Erythrocytes. A larger group of serums (281) were tested with chick erythrocytes after acetone-ether extraction as employed by Havens [6] and Morris [4,5] according to Porterfield's [8] modification of the method described by Casals and Brown [9]. The extracted serum was resuspended in a pH 9.0 borate buffer. The same buffer was used for serial dilutions of the serum in 0.5 ml. amounts, starting at 1:10 and carried through to 1:1280. Serums were kept at 2°c. to 4°c. in an ice bath during the dilution procedure. Chick cells were obtained by pooling the blood from six one day old chicks. They were collected and stored in Alsever's solution and washed three times in saline solution prior to use. As a 0.25 per cent suspension in a phosphate buffer (virus-adjusting diluent), they were added in equal volume to each serum dilution tube so that the resulting pH was 6.0. After vigorous shaking the cells were allowed to settle at 4°c. and agglutination patterns were read. The usual time required for this was three to four hours. Two different patterns of agglutination were observed, a rough granular pattern and, somewhat less commonly, a full or partial shield formation. In reading the test a titer of 1:80 or higher was considered to be positive, in accordance with Havens [6].

RESULTS

The results of hemagglutination tests performed with rhesus monkey cells according to the method of Hoyt and Morrison are listed in Table I. Serums from cases of hepatic disease of non-viral origin were uniformly negative and only one of the seven serums from patients with respiratory illness showed a titer considered to be positive (1:8 or higher). However, 50 per cent of the serums freshly obtained from laboratory personnel who were presumably normal individuals were found to be positive as compared with 54.5 per cent in the hepatitis group.

Agglutination tests with twenty serums from both the control and viral hepatitis groups rated positive by this test were made both before and after absorption of the serums with packed sheep erythrocytes, using rhesus monkey, sheep and one day old chick erythrocytes as the test system. (Table II.) Before absorption, sheep erythrocyte agglutinin titers were equal to or greater than rhesus erythrocyte agglutinins. After absorption with packed sheep erythrocytes, however, agglutination tests with rhesus erythro-

TABLE III

CHICK CELL HEMAGGLUTININ TITERS OF SERA FROM PATIENTS WITH VIRAL HEPATITIS, OTHER DISEASES, AND NORMAL CONTROL SUBJECTS

Serum Group	Reciprocals of Serum Hemagglutinin Titers							No. Positive* / No. Tested	Per cent Positive
	<40	40	80	160	320	640	1,280		
Viral hepatitis (stored <1 yr.):									
Acute (up to 2 wk.)	1	2	7	11	7	..	..	25/28	89
Convalescent (over 2 wk.)	4	1	14	7	2	..	2	25/30	83
Subtotal	5	3	21	18	9	..	2	50/58	86
Viral hepatitis (stored 2–6 yr.):									
Acute (up to 2 wk.)	5	4	6	1	..	1	1	9/18	50
Convalescent (over 2 wk.)	10	9	4	3	2	2	2	13/32	41
Subtotal	15	13	10	4	2	3	3	22/50	44
Other hepatic diseases:									
Cirrhosis	6	4	1	2	1	..	..	4/14	29
Jaundice, drug-induced	4	..	..	..	..	..	..	0/4	0
Obstructive jaundice	10	..	..	..	..	..	..	0/10	0
Non-hepatic diseases:†									
Malignancy	9	1	1	..	..	..	..	1/11	9
Collagen diseases	6	4	4	..	..	..	..	4/16	25
Gastrointestinal bleeding	7	1	..	..	..	..	..	0/8	0
Cardiovascular diseases	19	3	..	..	..	..	..	0/22	0
Infections, acute	9	1	..	1	..	..	..	1/11	9
Miscellaneous	32	9	3	1	1	..	..	5/46	11
Subtotal	82	19	8	2	1	..	..	11/114	10
Normal controls	25	4	2	..	..	..	..	2/31	6

* Titer of 1:80 or greater considered positive.

† All non-hepatitis serums were stored at −20°c. from a few days to a few weeks prior to testing.

cytes were all negative (less than 1:8). Some of the unabsorbed serums also agglutinated chick erythrocytes but with results that varied from those obtained with rhesus erythrocytes, i.e., titers were higher in some instances and lower in others. The titer of chick erythrocyte agglutinins was not significantly affected by absorption of the serums with packed sheep erythrocytes.

Of the 281 serums tested by the acetone-ether extraction method of Havens [6], using chick erythrocytes, 108 represented serums from fifty-six patients diagnosed as having viral hepatitis in varying stages of illness or convalescence. These have been divided on the basis of length of storage of the specimen prior to testing and on the basis of phase of the disease. The division between acute illness and convalescence was arbitrarily placed at a point two weeks after onset of symptoms. The remaining serums represent single specimens obtained from 139 patients with a variety of hepatic and other diseases, and thirty "normal" adults. The results of tests on all serums are presented in summary form in Table III.

Of the viral hepatitis serums stored at −20°c. for two to six years, only 44 per cent gave positive results. In contrast, of the hepatitis serums stored less than one year under the same conditions, 86.2 per cent were found to be positive. In no other group was such a high percentage of positive specimens noted.

Results obtained on a limited number of serial serum specimens from the same patients showed a decrease in the titer of agglutinins during convalescence in most instances and their ultimate disappearance in some. The inclusion of a few high titered convalescent serums in Table III tends to obliterate any suggestion of such a decrease. These serums were obtained from patients with chronic hepatic damage as a result of viral hepatitis.

Four of fourteen patients with hepatic cirrhosis had positive agglutinins in their serums. The four positive results were obtained in patients who had a history of prolonged alcoholism and malnutrition, histological evidence from biopsy of the liver or postmortem section typical of Laennec's cirrhosis, and clinical evidence of hepatic decompensation as manifested by increasing jaundice, edema, ascites or coma. Serums from patients with verified obstructive jaundice were consistently negative even at a dilution of 1:10. Four serums from patients with presumable drug-induced hepatitis (two received iproniazid and two chlorpromazine) were negative. Of sixteen patients with either lupus erythematosus or rheumatoid arthritis, four were found to have titers of 1:80, although none were higher. Serums from nineteen patients with cardiovascular disease (including ten cases of myocardial infarction with elevated serum glutamic oxalacetic transaminase levels) were all negative. Five of forty-six (10.9 per cent) serums from a miscellaneous group of hospitalized patients were found to be positive. These represented one case each of sarcoidosis (with hepatic infiltrations), infectious mononucleosis, multiple sclerosis and two cases of leukemia (of four tested). Of thirty-one serums from thirty normal subjects (laboratory personnel twenty to forty years of age) two were found to have titers of 1:80. One of these represented the second serum specimen obtained from a person with a previous titer of less than 1:10 and no known intervening illness.

Although most of the results presented are single tests on individual serums, approximately fifty have been repeated one or more times. Tests run on the same sample of extracted serum following storage at $-20°$ C. for up to one month are reproducible within one dilution, as are results using fresh extractions from whole serums stored under the same conditions. However extractions of serums stored for prolonged periods (over one year) tended to yield titers two or three dilutions lower than the level originally observed.

COMMENTS

The number of serums tested by the Hoyt-Morrison method was relatively small because the results of the first fifty-one serums tested failed to reveal a real difference between serums from patients with hepatitis and those from normal control subjects. No difference in titer was observed between acute and convalescent serums from the same patient with hepatitis.

Although titers of rhesus cell and sheep cell agglutinins were not equal, it is of interest that sheep cell agglutinin titers of twenty serums (both hepatitis and normal) rated positive by the rhesus agglutinin test were almost invariably higher than the rhesus agglutinin. Hoyt and Morrison included sheep cells in their original screening procedure and apparently did not observe such high sheep cell agglutinin titers. The difference between these observations may be an expression of the differences of agglutinability shown by erythrocytes from different sheep, as pointed out by Zarafonetis and Oster [*10*] in 1950. The fact that all tests with rhesus cells were negative after the serums had been absorbed with sheep cells would seem to indicate that the rhesus cell agglutinins are at least related to the sheep cell agglutinins, which have been shown to be present in a low titer in a fairly high percentage of normal human serums [*11*]. The presence of chick cell agglutinins in these unextracted serums did not appear to be related to either sheep or rhesus cell agglutinins. After absorption with sheep cells the chick cell agglutinins remained essentially unaltered in titer, and after acetone-ether extraction of the hepatitis serums in this group the chick cell titers (using the lower cell concentration of 0.25 per cent) increased fourfold or more, suggesting that some inhibitor had been removed.

The results obtained with the chick cell agglutinination test are in general agreement with those reported by Morris [*4,5*] and Havens [*6*]. The great majority of relatively fresh serums from patients with viral hepatitis, in both acute and convalescent stages of disease, contained these agglutinins in a titer of 1:80 or greater. The marked reduction in the number of positive results obtained using hepatitis serums which had been stored in the frozen state for prolonged periods is also in agreement with the suggestion

of Havens [6] that some labile factor seems to deteriorate on storage for these long periods.

Positive chick cell agglutinin titers were also observed in seventeen of the 170 non-viral hepatitis serums tested. These were concentrated primarily in two groups: cirrhosis (28.6 per cent positive) and collagen diseases (25 per cent positive). The total number of patients represented in each of these groups is relatively small, but those found to have positive titers at the time of testing were in an active phase of their disease process, e.g., decompensation in the case of those with cirrhosis.

Havens [6] was unable to demonstrate agglutinins in serums from patients with obstructive jaundice. In the present series of ten patients in this category, none had agglutinins. Similarly, serums from four patients with drug-induced jaundice (iproniazid or chlorpromazine) were negative.

On the basis of present results this test cannot be considered to be specific for viral hepatitis but it may well be of significant value in the differential diagnosis of jaundice.

The nature of the agglutinating substance or substances is not clear. Havens [6] has demonstrated that it is present in the gamma globulin fraction, and by the nature of the extraction procedure it would appear to be insoluble in lipid solvents. He also found that it is less heat-stabile than one would expect if it represented the virus itself. Beyond these suggestions its nature is still a matter of conjecture. It is evident that there is no relationship between agglutinin titers and bilirubin levels, and there is no apparent correlation with various liver function tests indicative of hepatocellular damage. The fact that serums from patients with myocardial infarction and associated serum transaminase elevations do not contain these agglutinins suggests that the reaction is not associated with this enzyme. However, it is possible that the titer of a given serum may depend upon a balance between agglutinins and as yet undefined inhibitors not removed by the extraction procedure. A negative result could represent an excess of the latter rather than an absence of the former. This possibility is given some support by very preliminary observations which suggest that some "negative" serums do, in fact, inhibit agglutination.

SUMMARY

Two recently described agglutination tests have been assessed for their possible value in studies concerned with human viral hepatitis. The rhesus erythrocyte agglutination test was not found to yield sufficiently significant results to make it a useful test. On the other hand, the chick-cell agglutination test, using acetone-ether extracted serum, gave results which showed a striking contrast between patients with viral hepatitis and those with a variety of other diseases or "normal" control subjects. Serums from patients with obstructive jaundice or drug-induced jaundice were uniformly negative.

The nature of these agglutinins is not clear, but their pattern of occurrence and mechanism of action deserve continued exploration.

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Liver Cell Necrosis in Chlorpromazine Jaundice (Allergic Cholangiolitis)*

A Serial Study of Twenty-Six Needle Biopsy Specimens in Nine Patients

SAMUEL ZELMAN, M.D.

Topeka, Kansas

THE general opinion expressed in numerous reports of cases of chlorpromazine jaundice is that hepatocellular damage is not found, either by laboratory or histologic evidence. Intrahepatic cholestasis, with its accompanying clinical and laboratory indications (hyperbilirubinemia, hyperphosphatasemia, hyperlipemia), and inflammatory infiltration of the portal areas are the findings universally agreed upon. More recently, rises in serum transaminases have been reported to occur in chlorpromazine jaundice. These reports seem to have led less to doubt of the absence of hepatocellular damage than to doubt of the significance of such rises in relation to liver cell damage.†

However, from the earliest reports, and since then increasingly, there have appeared dissenting observations of evidences of liver cell damage in this disease. In 1954 Zatuchni and Miller [*1*] described a patient in whom biopsy of the liver showed a mixed portal exudate extending into the adjacent hepatic parenchyma, with degeneration and phagocytosis of periportal liver cells. In 1955 similar findings were reported by Movitt et al. [*2*] in three cases in which small focal accumulations of inflammatory cells were found intralobularly. Similar accumulations or focal necroses were reported by Lemire and Mitchell [*3*], Gould et al. [*4*], Albacete et al. [*5*], and Hodges and LaZerte [*6*] (who also noted liver cell changes). Kelsey et al. [*7*] described biopsies of the liver in seven cases, and found evidences of liver cell degeneration in the central and mid-lobular zones, intralobular granulocytes singly and in small aggregates, and evidences of intralobular regeneration in four instances; hepatocellular disorganization with a heavy infiltration of inflammatory cells throughout the lobules in one case; and distorted lobular architecture due to fibrosis and regeneration in two. Grytting [*8*] reported "regressive changes and some interstitial inflammation in the liver tissue." Stacey et al. [*9*] found a decrease of glycogen in the liver cells in one case. Van Ommen and Brown [*10*] reported one case in which the liver cells were normal, but their published photomicrographs appear to indicate a wide area of centrolobular feathery degeneration of liver cells. While reporting no necrosis in one case, Mahaux and Vandecan [*11*] found evident regeneration of liver cells.

In 1956 Lindsay and Skahen [*12*] reported five cases in which centrolobular liver cell injury and regeneration were present. Central degeneration of liver cells was noted in one biopsy specimen and two autopsies by Stein and Wright [*13*]. Focal necroses were reported in biopsy specimens by Gants and Shadish [*14*], and Mitchell and Wilkinson [*15*]. DeVore et al. [*16*] found scattered pyknosis of liver cell nuclei in one biopsy specimen, and irregular reduction of intracellular glycogen in another. These authors noted depression of cholesterol esterification during the acute phase of icterus in two of four cases; the other two patients with initial low normal values of cholesterol esterifica-

† e.g. " . . . it is not certain that the increased serum enzyme levels reflect leakage of the enzyme into the blood from damaged liver cells. If this were the only mechanism for elevated transaminases in the blood, why should these levels be elevated in chlorpromazine jaundice, in which parenchymal damage is quite restricted?" (Editorial comment, Year Book of Medicine 1957–1958, p. 598. Chicago, 1957. Year Book Publishers.)

* From the Medical Service, Veterans Administration Hospital, Topeka, Kansas.

tion showed increases on recovery. Gambescia et al. [17] reported eight biopsies in six patients, noting isolated small areas of focal necrosis as part of the histologic pattern. Abnormal retention of bromsulfalein occurred in three of eight posticteric patients tested, and one patient had a positive serum cephalin cholesterol flocculation test. Elliott et al. [18] described a thirty-two year old woman in whom urticarial erythema, fever and eosinophilia developed on the twelfth day of chlorpromazine therapy. She was found dead the next day; autopsy showed "hepatomegaly with acute aseptic necrosis" of the liver.

In 1957 Werther and Korelitz [19] described liver biopsies in six cases, all showing evidence of centrolobular liver cell regeneration. These changes were interpreted as a result of concomitant liver cell loss even though direct histologic evidence of this was lacking. Benitez et al. [20] recorded unicellular degenerative changes and regeneration in one biopsy specimen; their Figure 2 suggests also that feathery necrosis was present. Two biopsy specimens were described by Skromak et al. [21] as showing "indistinct hepatic cells." Myers et al. [22] reported on one biopsy specimen in which there was centrolobular liver cell necrosis and regeneration, and "granulomatous areas" which may have been focal feathery necroses; their pictured area of large vacuolated "xanthoma cells" which "usually contained bile pigment" appears to be an area of feathery necrosis. Focal necroses were described in one biopsy specimen by Arias and Zamcheck [23]. Regeneration of liver cells was noted by Kessler et al. [24] in one biopsy, and is evident in a published photomicrograph of a biopsy specimen reported by Shay and Siplet [25]. The last-mentioned authors demonstrated increased bromsulfalein retention and rises in serum glutamic-oxaloacetic transaminase in their cases, but postulated seepage of enzymes from cells due to altered permeability rather than to necrosis.

In 1958 Gebhart et al. [26] reported nineteen biopsies in fifteen patients. They found ballooning degeneration of liver cells in eight biopsy specimens, multinucleation of liver cells in eighteen, mitoses in five, and necrosis of liver cells, including the production of Councilman-like bodies, in one. Bartholomew et al. [27] reported on two serial biopsy specimens, both showing destruction of periportal liver cells, including disappearance of some hepatic cords and partial collapse of the stroma in one area, as well as periportal focal necroses. In a fatal case of chlorpromazine jaundice recorded by Rodin and Robertson [28], a biopsy specimen obtained during life showed centrolobular unicellular liver cell degeneration and necroses, while at autopsy, eighteen days later, diffuse non-inflammatory centrolobular necrosis was found, "with preservation of the supporting reticulum," a picture suggesting feathery necrosis.

In a large psychiatric hospital the patients referred to me with chlorpromazine jaundice have generally been available for prolonged hospital observation, and have been subjected to intensive serial clinical laboratory and biopsy studies. Not all patients in whom chlorpromazine jaundice developed at this hospital were so studied, for some were not sufficiently ill or proved uncooperative. Nine cases were studied in sufficient detail to warrant inclusion in this report. Since my experience would indicate that liver cell damage is usual in this disease, a report of these observations seems indicated. (Table 1.)

These nine patients had a total of twenty-six needle aspiration biopsies of the liver during the course of allergic cholangiolitis following administration of chlorpromazine. One patient (Case 9) provided five biopsy specimens, two patients (Cases 3 and 6) provided four specimens each, two patients (Cases 1 and 2) three specimens each, three patients (Cases 4, 5 and 8) two specimens each, and one patient (Case 7) a single biopsy specimen. All biopsies were performed percutaneously and intercostally, using the Roth-Turkel needle. Biopsied tissue was immediately fixed in formalin. Sections were cut at 8 microns' thickness, and routinely stained with hematoxylin and eosin. Special stains used included van Gieson, iron and reticulum stains. The earliest biopsy specimen obtained was on the fourth day of illness (Case 9), the latest sixteen months after the onset (Case 9).

CASE PROTOCOLS

CASE 1. On the nineteenth day of chlorpromazine therapy, a fifty-four year old white man became acutely ill with chills, fever which reached temperatures as high as 104.4°F., and symptoms and signs suggestive of "asthmatic bronchitis." The leukocyte count was not increased, but a left shift was present in the differential count, and there was some elevation of the erythrocyte sedimentation rate. Eosinophilia was not recorded. Fever lasted until the seventh day, and on the eighth day jaundice and tenderness of the

TABLE 1

PERTINENT LABORATORY DATA IN NINE CASES OF CHLORPROMAZINE JAUNDICE

Data	Unit	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Peak eosinophilia (day)	% or per mm.[3]	.....	1,460 (18)	.....	495 (137)	1,075 (7)	7% (11)	9% (2)	29% (4)	1,620 (4)
Peak serum bilirubin (day)	Mg. %	19.0 (11)	12.0 (18)	25.3 (28)	8.6 (16)	1.9 (7)	6.0 (12)	4.2 (2)	6.8 (11)	11.0 (8)
Duration of icterus	Days	82	93	115+	60	7	31	21	24	50
Peak serum alk. phosphatase (day)	Bodansky	98.0 (22)	38.4 (18)	24.6 (29)	27.9 (17)	7.6 (8)	31.7 (13)	17.3 (9)	31.5 (15)	33.0 (15)
Duration of hyperphosphatasemia	Days or mo.	4½+ mo.	5½+ mo.	18+ mo.	59 days	22 days	6+ mo.	58+ days	43 days	18+ mo.
Peak total serum lipid (day)	Gm. %	.....	.....	.....	0.83 (58)	0.70 (15)	2.12 (20)	.....	1.03 (37)	0.95 (75)
Low total serum lipid	Gm. %	.....	.....	.....	.....	0.53	1.21	.....	0.72	0.72
Peak serum cholesterol (day)	Mg. %	720 (28)	306 (31)	324 (262)	325 (38)	232 (15)	309 (13)	336 (9)	300 (36)	376 (30)
Low serum cholesterol	Mg. %	262	234	182	247	143	267	239	192	239
Peak serum G-O transaminase (day)	Karmen	.....	.....	47 (18)	94 (19)	38 (10)	.....	20 (9)	110 (11)	142 (10)
Peak serum G-P transaminase (day)	Wroblewski	.....	.....	37‡ (200)	.....	55 (11)	265 (12)	55 (9)	170 (11)	318 (12)
Peak non-cholestatic* BSP retention (day)	%	6 (67)	18 (80)	.....	7 (60)	.....	8 (26)	24 (10)	N	26 (43)
Peak 24 hr. serum cephalin flocc. (day)	1–4 plus	3 (60)	N	N	2 (30)	2 (7)	N	1 (9)	N	4 (43)
Peak serum thymol turbidity (day)	Maclagan	N†	12 (165)	N	5.5 (51)	6 (16)	N	N	N	N
Peak serum gamma globulin (day)	Gm. %	N	N	1.5 (28)	1.5 (16)	1.45 (16)	N	.....	N	N
Low % esterified serum cholesterol (day)	%	45 (19)	N	42 (52)	41 (52)	N	N	58 (28)	51 (29)	30 (10)
Peak prothrombin time Quick (day)	Sec.	N	N	N	N	13.8 (7)	N	N	13.2 (11)	15 (2)
Length of observation	Days or mo.	37 mo.	11 mo.	18 mo.	14 mo.	53 days	6 mo.	58 days	43 days	18 mo.

* Less than 1 mg. one-minute direct reacting bilirubin.

† N = Normal value.

‡ Not available earlier.

liver were discovered. Weakness, anorexia and weight loss continued during the next three weeks, followed by symptomatic recovery.

On the eleventh day of illness the serum bilirubin was 19.0 mg. per cent, of which 10.0 mg. was one-minute direct reacting. The serum total bilirubin fell progressively thereafter, reaching normal levels by the eighty-second day. Bile was found in the urine until the fifty-third day. The serum alkaline phosphatase on the eleventh day of illness was 52.9 Bodansky units. It rose progressively to a peak of 98 units on the twenty-second day, falling progressively thereafter to 8.1 units on the ninetieth day; subsequent fluctuations varied between 7.3 and 18.9 units over the next four and one-half months during which the patient was followed up. The serum cholesterol was 364 mg. per cent on the eleventh day of illness, rising progressively to a peak value of 720 mg. on the twenty-eighth day, and falling progressively thereafter to reach 262 mg. per cent on the 102nd day.

Although the zinc and thymol turbidity tests remained within normal limits throughout the course of illness, the serum cephalin cholesterol flocculation test varied from 1 to 3 plus in twenty-four hours, returning to a normal reading only after 200 days. The serum albumin and globulin were not disturbed. Esterification of the serum cholesterol varied between 45 and 58 per cent during the first month of illness, and between 59 and 70 per cent thereafter. Bromsulfalein retention at forty-five minutes was 6 per cent on the sixty-seventh day.

Roentgen visualization of the liver and spleen [*29*] was performed on the eleventh and thirty-ninth days, and again seventeen months after the onset of illness. This showed considerable enlargement of the liver on the thirty-ninth day, not present in either the initial or final studies.

Needle biopsy specimens of the liver were obtained on the eleventh, twenty-fifth and 117th days of the illness. The initial biopsy specimen (Figs. 1A and 1B) showed widening of the centrolobular sinusoids, which were infiltrated with phagocytes predominantly mononuclear in some areas but polynuclear as well, and including eosinophilic granulocytes in others. There were many fine branching intracanalicular bile plugs in the centrolobular zones, but more prominent was the intracytoplasmic granular deposit of bile pigment in the centrolobular liver cells. Many of these cells showed degenerative changes, including hyalinization, lysis, unicellular feathery necrosis and nuclear pyknosis. Some shedding of shrunken hyalinized liver cells into the sinusoids (Councilman-like bodies) was seen. A moderate number of lipochrome-filled Kupffer cells were noted in the centrolobular zones. Regeneration was evident in the frequent appearance of mitotic figures in liver cells of this zone, and the wide variation in size of liver cells and their nuclei, with multiple nucleoli, as well as the appearance of multinucleated cells. One tripolar mitosis was seen.

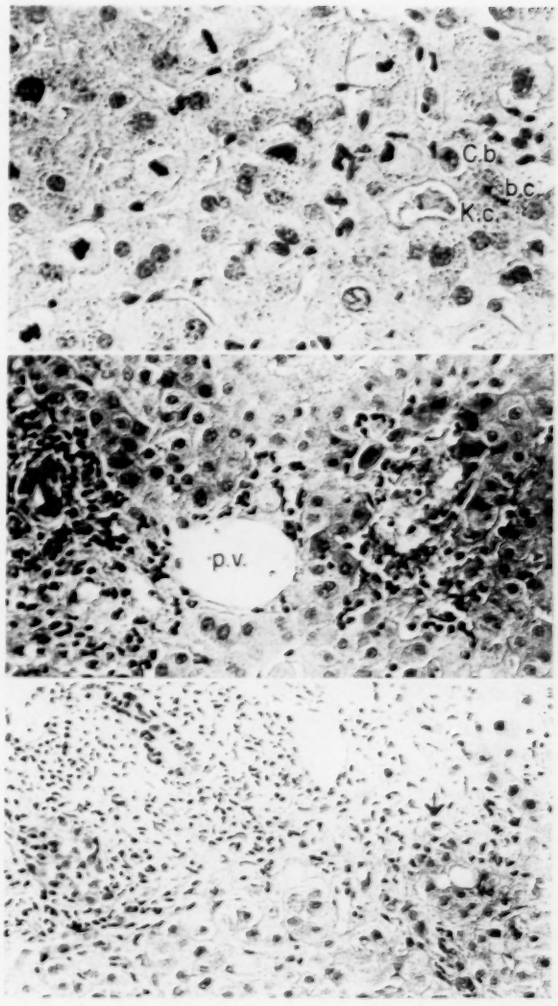


FIG. 1. A, Case 1, eleventh day. Chlorpromazine jaundice, centrolobular zone. Cholestasis is evident chiefly intracytoplasmically but also intracanalicularly (b.c.). An intrasinusoidal Councilman-like body is seen (C.b.), and one lipochrome-engorged Kupffer cell (K.c.). Five mitotic figures are seen in this field. Large cells with multiple nucleoli, and multinucleated cells, are also indicative of regeneration. Hematoxylin and eosin, × 280. B, Case 1, eleventh day. Chlorpromazine jaundice, portal area. A fairly large area of coagulative necrosis and dissolution of liver cells is seen adjacent to a portal vein (p.v.). A mixed cellular infiltrate containing many eosinophilic granulocytes fills the portal space at left, and has invaded the wall of a small bile duct at upper left. Hematoxylin and eosin, × 210. C, Case 1, twenty-fifth day. Chlorpromazine jaundice, portal area. A portal area with mixed cellular infiltrate including eosinophils is bordered below and at right by feathery dissolution of periportal liver cells. Note destruction of terminal liver cell plate in these regions. A disorganized bile duct is seen at left, a small partially necrotic bile duct at right (arrow) and a regenerating bile duct above. Hematoxylin and eosin, × 135.

Focal necroses were found both centrolobularly and periportally. A mixed cellular infiltrate containing

large and small mononuclear cells, and polynuclear cells including moderate numbers of eosinophils, crowded the portal spaces and in some areas invaded periportally. Interlobular bile ducts were few and appeared disorganized.

The second biopsy specimen was obtained two weeks later, on the twenty-fifth day of illness. The central sinusoids were now less wide, and sinusoidal infiltrations more focal than diffuse. Unicellular necroses were in greater evidence, and small focal necroses bordered some of the central veins. Bile pigment was more prominent, constituting larger and deeper staining canalicular plugs, and filling many Kupffer cells, while liver cell cytoplasmic retention of bile pigment granules persisted. Mitotic figures were no longer found in liver cells, but centrizonal regeneration was still apparent in multiple nucleation, and in varying size of cells and their nuclei. Focal necroses were seen both centrally and periportally, as before. In addition, many periportal areas showed feathery necrosis. (Fig. 1C.) While the portal infiltrate had subsided somewhat, and eosinophilic granulocytes appeared less frequently, there were accumulations of fibroblasts and deposit of collagen in many portal areas, and the cellular infiltrations appeared more often to infiltrate the periportal zones. The cellular infiltrations continued mixed, containing lymphocytes, mononuclear and polynuclear cells. Interlobular bile ducts were abundantly present and regenerating, but continued to show evidences of disorganization. (Fig. 1C.)

The third biopsy specimen was obtained at the end of four months of illness (117th day). The centrolobular zones continued to show intracytoplasmic bile pigment granules in liver cells, but there was no canalicular plugging. Kupffer cells were still prominent and many of them contained pigment but other phagocytes were few. Degenerative changes remained evident in the centrizonal liver cells, some showing fading and others homogenation of cytoplasm, while their nuclei showed lysis or pyknosis or more often vacuolation, but actual necrosis of liver cells was not frequent. The liver cells continued to vary in cell size and nuclear size in this zone. Focal necroses were found infrequently in the central zones. The portal areas were small and densely collagenous with a tendency to stellate arrangement. They were infiltrated only with small round cells. The bile ducts were within normal limits.

Three years and one month after the onset of his chlorpromazine jaundice, the patient died of Asian influenza complicating pulmonary emphysema. At autopsy the liver showed the usual agonal and postmortem centrolobular stasis and atrophy, with cytoplasmic bile pigment retention and focal necroses. The portal areas appeared normal.

Comment: Necrosis and active regeneration of liver cells of the centrolobular zones and to less extent of the periportal zones were prominent in biopsy specimens obtained on the eleventh and twenty-fifth days of chlorpromazine jaundice. Mitotic figures were particularly numerous on the eleventh day. Interlobular bile ducts were scanty and disorganized on the eleventh day and actively regenerating on the twenty-fifth day. Portal fibrosis found at the end of the fourth month was no longer present at autopsy three years later.

Case 2. On the ninth day of chlorpromazine therapy, fever, generalized aching, right hypochondric pain and nausea developed in a thirty-two year old white man. Pruritus appeared nine days later, associated with visible icterus and a tender liver edge palpable 4 cm. below the costal margin. Enlargement of the liver was evident by roentgen visualization on the seventeenth day of the illness. The symptoms gradually subsided over a period of three weeks, and the patient left the hospital against advice on the thirty-second day.

A leukocyte count obtained on the second day of illness showed a left shift but normal total count, and included 2 per cent eosinophils. The eosinophils rose to 7 per cent on the thirteenth and 22 per cent on the seventeenth day. A chamber eosinophil count on the eighteenth day was 1,460 per cu. mm., and subsequent chamber counts fell progressively to 672 per cu. mm. on the thirty-second day. The erythrocyte sedimentation rate was elevated.

The serum bilirubin was 2.8 mg. per cent, of which 1.2 mg. was one-minute direct reacting, on the third day of illness. It rose progressively to a peak of 12.0 mg. per cent, of which 4.6 mg. was direct reacting, on the eighteenth day; and fell progressively thereafter to 5.0 mg. per cent (1.8 mg. direct) on the thirtieth day. The serum alkaline phosphatase was 7.4 Bodansky units on the third day, rose progressively to a peak of 38.4 units on the eighteenth day and fell progressively thereafter to 16.3 units on the thirtieth day. The serum cholesterol was 234 mg. per cent on the third day, 260 mg. per cent on the eighteenth day and 306 mg. per cent on the thirty-first day.

After leaving the hospital the patient returned to his work at a metal foundry and worked four nights; then he became nauseated again and right hypochondric pain developed. Jaundice did not increase. He was hospitalized elsewhere from the forty-fifth to sixtieth days, with subsidence of jaundice, pain and nausea. He returned to work but pain recurred after one week, although without nausea or jaundice. After working a second week despite pain, the patient was rehospitalized here. During this period out of the hospital he had reverted to weekend alcoholism (as many as ten beers per weekend). Upper respiratory inflammatory symptoms had been present for three weeks preceding readmission.

Readmitted on the seventy-ninth day of illness, the patient was found to have a tender liver edge palpable 5 cm. below the costal margin, and telangiectasia of the neck and chest but no actual "spiders." His temperature and total and differential leukocyte count were normal, but the erythrocyte sedimentation rate was elevated. On the eightieth day of illness the serum bilirubin was 1.5 mg. per cent, of which 0.4 mg. was one-minute direct reacting, and fell to 0.6 mg. per cent by the ninety-third day. The serum alkaline phosphatase varied between 17.1 and 9.6 Bodansky units, in general following a progressive decrease. The serum cholesterol was 240 mg. per cent, normally esterified. The serum albumin and globulin were normal, but the gamma globulin was 1.9 gm. per cent and the cephalin cholesterol flocculation test 1 plus in twenty-four hours. The thymol turbidity varied between 5.0 and 8.5 units during the eightieth to 107th days, between 3.5 and 4.5 units thereafter until the 143rd day, when the patient indulged in a bout of alcoholism, and rose progressively thereafter to 12 units on the 165th day, when he was discharged from hospital. The serum bromsulfalein retention at forty-five minutes was 18 per cent on the eightieth day and 6 per cent on the eighty-eighth day.

Five months later, at another hospital, the patient's serum showed normal values for thymol turbidity, cephalin cholesterol flocculation and alkaline phosphatase, as well as bilirubin and bromsulfalein retention.

Needle biopsy specimens of the liver were obtained on the thirteenth day of illness during the first hospitalization, and on the eighty-first and 139th days during the second hospitalization. In the initial biopsy specimen there were wide centrolobular zones of dilated sinusoids containing many scavenger cells. There were many small intracanalicular bile plugs. The liver cells of this zone showed intracytoplasmic bile pigment, many with degenerative changes; there were occasional unicellular liver cell necroses and evidences of cellular regeneration. The portal areas showed a rich infiltration with mixed mononuclear and polynuclear inflammatory cells, including numerous eosinophilic granulocytes. In some areas this exudate had broken through the limiting plate and invaded the periportal lobular zones.

In the second biopsy specimen, obtained on the eighty-first day, the centrolobular zones presented a more nearly normal appearance but intracanalicular bile plugs were still frequent and degenerative and regenerative changes in liver cells were still apparent. Phagocytes were few in the sinusoids, which were no longer widened, but lipochrome-filled Kupffer cells were more prominent. Occasional small inflammatory focal necroses were seen in these zones. One large area of feathery necrosis (Fig. 2A) was found in a centrolobular position. A loose infiltration of mononuclear and polynuclear inflammatory cells in this necrotic area included many eosinophils. The

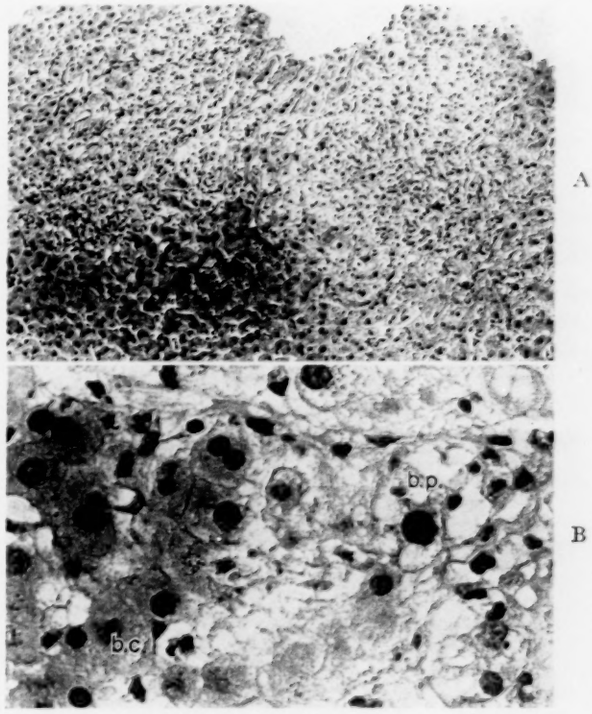


FIG. 2. A, Case 2, eighty-first day. Chlorpromazine jaundice, centrolobular zone. A large dumbell-shaped area of feathery necrosis is sparsely infiltrated by mixed inflammatory cells including eosinophils. Hematoxylin and eosin, × 70. B, Case 2, eighty-first day. Transitional zone at edge of necrotic area pictured in (A). There is a gradual transition from regenerating liver cells at left to complete dissolution with ghost-like residual reticulated networks at right. Intracytoplasmic (b.p.) and intracanalicular (b.c.) bile pigment is present in moderate abundance. Hematoxylin and eosin, × 350.

necrosis merged gradually into normal liver parenchyma; the bordering cells (Fig. 2B) showed varying degrees of lysis and cytoplasmic vacuolation, and were especially rich in cytoplasmic bile pigment. The portal areas were nearly free of the previous inflammatory infiltrate, but now showed a definite fibrosis not previously present. In one periportal area, inflammatory exudate persisted among necrotic liver cells.

The third biopsy specimen was taken on the 139th day of illness (four and one half months). An occasional centrolobular bile plug persisted. The centrizonal liver cells showed continued variation in size of cells and nuclei, and many nuclei were vacuolated. The portal areas continued fibrosed, and contained a sprinkling of mononuclear and polynuclear inflammatory cells.

Comment: This case was complicated by periods of muscular work and weekend alcoholism after the first month of illness. Relapse of illness involved recurrence of hepatic pain and tenderness without exacerbation of jaundice. A large

area of feathery necrosis appeared in the biopsy specimen of the liver nearly three months after the onset, and well defined portal fibrosis replaced the original portal infiltrate.

CASE 3. On the twelfth day of chlorpromazine therapy a thirty-six year old white man became ill with fever, sore throat, cough and anorexia. Thirteen days later, jaundice and a tender liver palpable 3 cm. below the costal margin were noted. Vomiting, diarrhea and lethargy occurred during the next few days. Pruritus was noted on the twenty-first day of the illness and became so intractable by the thirty-ninth day that methyltestosterone therapy was used. The pruritus subsided and the methyltestosterone therapy was discontinued one week later. Adrenocorticoid therapy was instituted from the twenty-eighth to sixty-seventh days, approximately one month. Because of behavioral difficulties, bedrest was never maintained. Moderate enlargement of the liver and slight enlargement of the spleen were noted by roentgen visualization on the twenty-second day of illness.

Eosinophilia was not present on the eighteenth day of illness or thereafter; earlier observations were not available. The serum bilirubin on the fifteenth day was 15.0 mg. per cent, of which 6.5 mg. was one-minute direct acting. The serum total bilirubin rose to 25.3 mg., of which 6.8 mg. was direct, on the twenty-eighth day, falling gradually thereafter to reach normal levels by the 115th day. Minor increases in serum bilirubin occurred irregularly thereafter, involving both direct and indirect reacting fractions, as late as nine months after the onset of illness. Bile was found in the urine through the fifty-first day of illness. Urine urobilinogen by the semiquantitative method remained normal.

The serum alkaline phosphatase was 20.6 Bodansky units on the fifteenth day and reached 24.6 units on the twenty-ninth day; subsequent observations over a period of eighteen months after the onset of illness indicated fluctuation between 8.6 and 28.3 Bodansky units, the final value when the patient was dropped from observation being 10.3 units. The serum cholesterol ranged from 182 to 319 mg. per cent with no apparent pattern of change. The serum albumin and globulin were normal on the fifteenth day. The serum gamma globulin was 1.0 gm. per cent on the eighteenth day, rose to 1.5 gm. on the twenty-eighth day and fell again to 0.9 gm. per cent on the fifty-first day. Concomitantly, the thymol turbidity measured 1.5 units on the fifteenth day, 3.5 units on the twenty-eighth day and 1.0 unit on the thirty-ninth day. The serum cephalin cholesterol flocculation test remained negative. The esterified fraction of serum cholesterol varied between 42 per cent and 57 per cent through the first two months of illness, and between 58 and 80 per cent thereafter. The serum glutamic-oxaloacetic transaminase was 47 units on the eighteenth day and normal thereafter. The serum glutamic-pyruvic transaminase was not available until the 200th day of illness, and was then 37 units; later values were normal.

Needle biopsy specimens of the liver were obtained on the twenty-second, forty-ninth, eighty-fifth and 207th days of the illness. The initial biopsy specimen (at three weeks) showed cholestasis with bile canalicular plugging and intracytoplasmic liver cell and Kupffer cell accumulations of bile in a wide centrolobular zone. Non-inflammatory degeneration and lysis of neighboring liver cells were prominent, with disruption of many liver cell plates. The mid-lobular zones showed active liver cell regeneration and a fine vacuolated appearance of the cytoplasm of many liver cells. A moderate mixed cellular infiltrate was present in the portal areas and extended into the sinusoids of the central zones. Eosinophils were not seen.

The second biopsy specimen, obtained at seven weeks, was distinguished from the first in showing more prominent focal inflammatory necroses in the centrolobular zones, increased evidence of liver cell regeneration with polynucleation up to 5 nuclei, prominence of lipochrome-engorged Kupffer cells and diminished portal infiltrate. The wide centrolobular zones of liver cell degeneration and necrosis persisted, with hyalinization of cytoplasm, nuclear pyknosis and cellular lysis. Centrolobular cholestasis appeared little changed. (Fig. 3A.)

In the third biopsy specimen, obtained at three months, the centrolobular zones continued to show plugged bile canaliculi but these were no longer numerous. The centrolobular liver cells now appeared intact except for isolated unicellular eosinophilic shrinkage and nuclear pyknosis. Two or three small multicellular focal inflammatory necroses were found in nearly every centrolobular zone. (Fig. 3B.) Lipochrome-filled Kupffer cells were prominent. Evidences of regeneration were less marked and the portal areas appeared normal.

The fourth biopsy specimen was obtained seven months after the onset of illness. An occasional bile canalicular plug remained in the centrolobular zones but no liver cell necrosis was evident. Variation in size of liver cells and their nuclei persisted. A slight portal fibrosis was noted.

Comment: Liver cell necrosis and regeneration were most prominent in the second biopsy specimen, taken seven weeks after the onset of chlorpromazine jaundice, when the serum bilirubin and alkaline phosphatase were near their peak values. Necrosis was still evident at three months, and there was slight regeneration at seven months. Clinical improvement coincided with the use of adrenocorticoid therapy during the second month, but the laboratory and histologic course seemed unaffected.

CASE 4. On the thirtieth day of chlorpromazine therapy, a forty-four year old white woman was noted to be jaundiced and moderately febrile. She related a two-week history of slight anorexia and nausea, weakness and dizziness, and intermittent diarrhea. The liver was enlarged and tender, its enlargement confirmed by roentgen visualization.

Five per cent eosinophils had been recorded in a differential leukocyte count on the eighth day of chlorpromazine therapy (eight days prior to onset of symptoms), previous determinations having never been more than 2 per cent. Further counts were not available until the sixteenth day of the illness. Subsequent chamber eosinophil counts ranged between 182 and 481 per cu. mm. during the first two months, and between 255 and 495 per cu. mm. over an additional year during which the patient was observed.

On the sixteenth day of illness (calculated from the patient's history of symptoms) the serum bilirubin was 8.6 mg. per cent, of which 3.8 mg. was one-minute direct reacting. This decreased progressively in serial determinations to reach normal levels by the end of the second month. Bile was found in the urine initially, but urobilinogen was not increased. The serum alkaline phosphatase was 27.9 Bodansky units on the seventeenth day of illness, falling progressively thereafter to reach 6 units at the end of the second month (fifty-ninth day). The serum cholesterol varied between 247 and 325 mg. per cent, without significant trend during this period.

The serum cephalin flocculation test was 1 or 2 plus in twenty-four hours during the first month of illness, and negative thereafter. The serum thymol turbidity was 2.4 units initially, but was recorded as 5.5 units on the fifty-first day. The serum gamma globulin was 1.5 gm. per cent on the sixteenth day of illness, 1.4 gm. per cent on the twenty-third and thirtieth days and 1.1 gm. per cent on the thirty-ninth day. The serum albumin and globulin, and serum iron, were normal, and the serum C-reactive protein was negative on the sixteenth day. The ratio of esterified serum cholesterol was over 60 per cent in all but one determination, 41 per cent being recorded on the fifty-second day. The serum glutamic-oxaloacetic transaminase was 52 units on the sixteenth day of illness, rising to a peak of 94 units on the nineteenth day and falling progressively thereafter to reach normal values at the end of the first month of illness. Bromsulfalein retention was 7 per cent in forty-five minutes on the sixtieth day.

Needle biopsy specimens of the liver were obtained on the nineteenth and sixtieth days of illness. In the initial biopsy the centrolobular zones showed accumulated bile pigment within the cytoplasm of liver cells, and inspissated bile plugs in biliary canaliculi. Unicellular bile necroses, eosinophilic shrinking and hyalinization, and lysis of liver cells were seen in these zones. Occasional Councilman-like acidophilic bodies were seen in the sinusoids. Lipochrome-containing Kupffer cells were found centrolobularly, occasionally

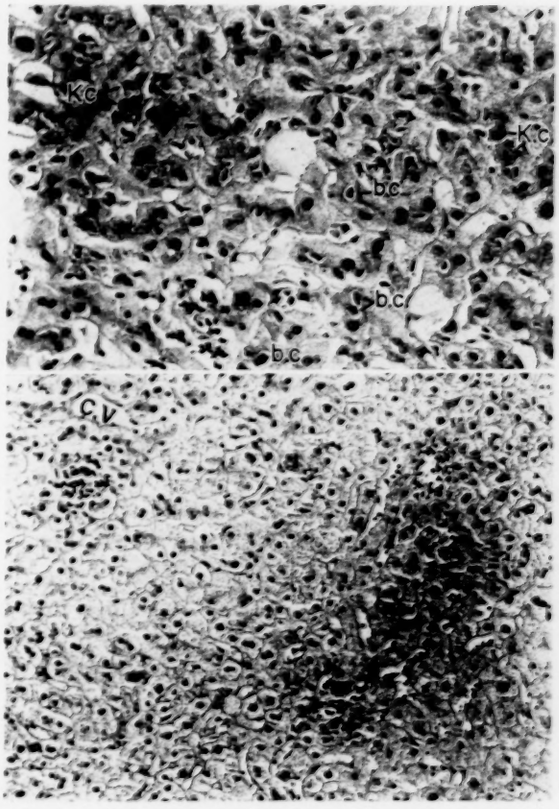


FIG. 3. A, Case 3, forty-ninth day. Chlorpromazine jaundice, centrolobular zone. Diffuse coagulative necroses and feathery vacuolation of liver cells, with occasional bile necrosis (disintegration of bile-choked liver cell). Bile-filled and lipochrome-filled Kupffer cells (K.c.) are prominent. Note disturbed arrangement and occasional disruption of liver cell plates. The feathery vacuolation, paucity (none in this field) of acidophilic bodies, and relatively intact liver cell plates distinguish this picture from that of viral hepatitis. A superficial resemblance to fat vacuolation is produced by ballooning and feathery vacuolation of liver cells. b.c. = canalicular bile plugs. Hematoxylin and eosin, ×160. B, Case 3, eighty-fifth day. Chlorpromazine jaundice, centrolobular zone. One focal necrosis lies below the central vein (c.v.), at upper left; two additional focal necroses at right are at opposite ends of a large area of coagulative liver cell degeneration and necrosis, with sinusoidal infiltration. Occasional lipochrome-filled Kupffer cells are seen centrally, and liver cell regeneration is evident in peripheral portions of the field. Hematoxylin and eosin, × 105.

in focal collections. The sinusoids in some areas were infiltrated by granulocytes, and occasional focal necroses were found, predominantly centrolobularly. (Fig. 4.) Active liver cell regeneration was indicated by variation in size of cells and frequency of double nuclei. The portal spaces were infiltrated by a pleomorphic cellular exudate containing many eosinophilic granulocytes; in some areas this infiltrate extended into the periportal lobular zones.

In the second biopsy specimen, obtained on the

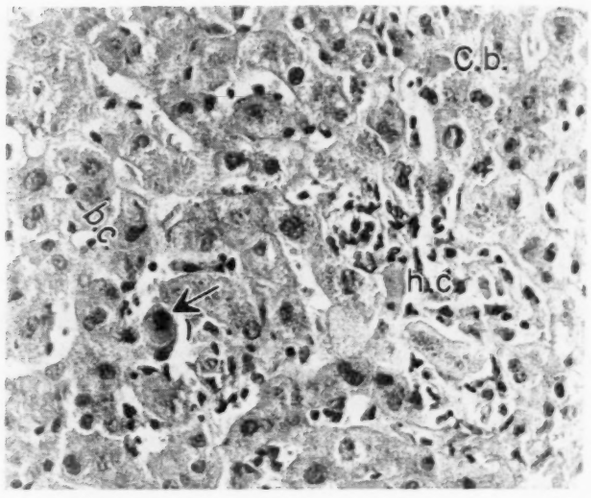


FIG. 4. Case 4, nineteenth day. Chlorpromazine jaundice, centrolobular zone. Moderately large area of focal necrosis. Note hyalinized and shrunken liver cell (h.c.), acidophilic body in sinusoid (C.b.), and larger hyalinized cell with pyknotic nucleus in sinusoid engulfed by Kupffer cell (arrow). The canalicular bile plugs (b.c.) are small and lightly stained. Hematoxylin and eosin, × 230.

sixtieth day, inflammatory activity had largely disappeared, but active liver cell regeneration persisted throughout the lobules. Lipochrome-filled Kupffer cells were present in the centrolobular zones. Intracytoplasmic bile granules were present in the centrolobular liver cells, but only rarely was a bile plug found in a canaliculus. Cellular necrosis and degeneration were no longer present.

Comment: Centrolobular and some periportal liver cell necrosis were present on the nineteenth day of chlorpromazine jaundice, when the serum glutamic-oxaloacetic transaminase was at its peak value of 94 units, and the serum bilirubin and alkaline phosphatase were close to the highest levels reached.

CASE 5. On the sixth day of chlorpromazine therapy, malaise, weakness and nausea developed in a twenty-eight year old white man. Fever, vomiting and muscle aching supervened two days later. There was generalized muscle tenderness and more specific tenderness of the liver edge, which was palpable at the chondric margin. Clinical icterus was not apparent. Symptoms gradually subsided during the next few days.

The leukocyte count was not increased but there was a left shift in the differential count. A routine leukocyte count taken on the day before onset of illness had revealed 7 per cent eosinophils. A chamber eosinophil count on the seventh day of illness was 1,075 per cu. mm.; this dropped to 692 on the twenty-second day, and 4 per cent eosinophils in the differential count persisted on the fifty-third day, when the patient was dropped from observation.

The serum bilirubin was 1.9 mg. per cent on the seventh day, 0.4 mg. of this being one-minute direct reacting; later determinations were normal. Bile was found in the urine only in trace amounts during the fourth, fifth and sixth days, and was absent thereafter. Urobilinogen was increased in the urine to 2.6 Ehrlich units in a two-hour specimen on the seventh day but was normal thereafter.

The serum alkaline phosphatase was 7.6 Bodansky units on the eighth day and 7.3 units on the fifteenth day, falling to 4.6 units on the twenty-second day. The serum cholesterol and the total lipids increased from 143 and 528 mg. per cent, respectively, on the seventh day to 232 mg. and 698 mg. per cent on the fifteenth day.

The serum cephalin cholesterol flocculation test was 2 plus in twenty-four hours on the seventh day, 1 plus on the fifteenth day and negative thereafter. The thymol turbidity was 2.5 units on the seventh day, rose to 6 units on the sixteenth day, and fell to 4.9 and 4.1 units on the twenty-third and thirty-seventh days. The serum gamma globulin was 1.2 gm. per cent on the seventh day, rose to 1.45 gm. on the sixteenth day and fell to 1.39 gm. on the twenty-third and 1.23 gm. on the thirty-seventh days. The serum glutamic-oxaloacetic transaminase fluctuated between 6 and 28 units, never rising above normal, but the serum glutamic-pyruvic transaminase varied from 26 to 55 units, reaching normal values on the fifteenth day. The fluctuations of the two transaminases were parallel. (Fig. 5.) An initial slight prolongation of prothrombin time was recorded.

Needle biopsy specimens of the liver were obtained on the eighth and forty-second days of illness. Mild bile peritonitis occurred after the second biopsy. The initial biopsy showed a fine granular bile pigment accumulation in the cytoplasm of liver cells, especially along the bile canalicular margins, and filling bile canaliculi, in the centrolobular zones. Many pericentral liver cells showed feathery necrosis, and occasional multicellular focal necroses were present. The portal triads were moderately infiltrated with a pleomorphic cellular exudate rich in eosinophils. In some areas this infiltrate had disrupted the laminar plate and invaded the lobule to cause periportal necrosis of liver cells. (Fig. 6.)

The second biopsy specimen, obtained six weeks after the onset of illness, showed mild diffuse damage and regeneration of the centrolobular liver cells, with an occasional small focus of necrosis, and a few Kupffer cells filled with lipochrome, in the central zones. Cholestasis was no longer present and the portal infiltrations largely subsided.

Comment: Although this was a mild case of chlorpromazine jaundice, the liver biopsy on the eighth day showed centrizonal and periportal

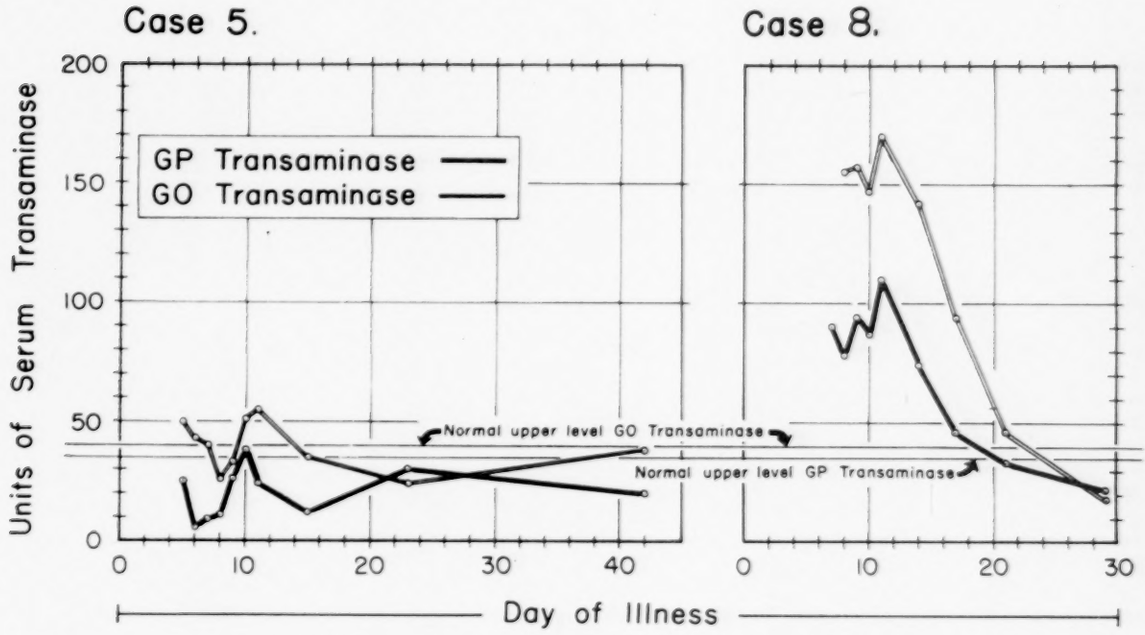


FIG. 5. Serum transaminase curves in mild (Case 5) and moderately severe (Case 8) cases of chlorpromazine jaundice. Note that the two transaminase curves run parallel, but that the levels of glutamic-pyruvic transaminase exceed those of glutamic-oxaloacetic transaminase. Increased severity is reflected in higher and more prolonged elevations. (Compare with Figure 9.)

necrosis of liver cells. Of interest are the minor transient rises in serum flocculation and turbidity indices, and in the two serum transaminases. (Fig. 5.)

CASE 6. After three weeks of chlorpromazine therapy, a thirty-eight year old white man became ill with epigastric pain, nausea, some generalized pruritus and jaundice, with dark urine and light stools. When seen on the eleventh day of illness he was mildly icteric, had a slow regular pulse, a tender liver edge palpable 5 cm. below the costal margin, referred liver tenderness on compression of the right rib cage, and lymph nodes in the axillas and groin. Both liver and spleen showed slight enlargement when visualized by x-ray examination on the eighteenth day. Therapy consisted of bedrest, nutritional support and prednisolone administered between the seventeenth and thirty-third days. Symptomatic improvement was prompt.

A differential leukocyte count on the eleventh day of illness included 7 per cent eosinophils but subsequent chamber eosinophil counts did not exceed 270 per cu. mm. Bile was found in the urine on the eleventh day of illness but soon disappeared. The serum bilirubin on the twelfth day was 6.0 mg. per cent, of which 2.0 mg. was one-minute direct reacting. Two days later the serum bilirubin had dropped to 1.6 mg. per cent, but following the introduction of prednisolone therapy it rose to 2.4 mg. on the twentieth day, the increase involving only the direct reacting fraction, and fell progressively thereafter to reach normal levels by the thirty-first day. Urobilinogen was not increased in the urine.

The serum alkaline phosphatase was 31.7 Bodansky units on the thirteenth day, falling progressively thereafter to 12.5 units one month after the onset of illness

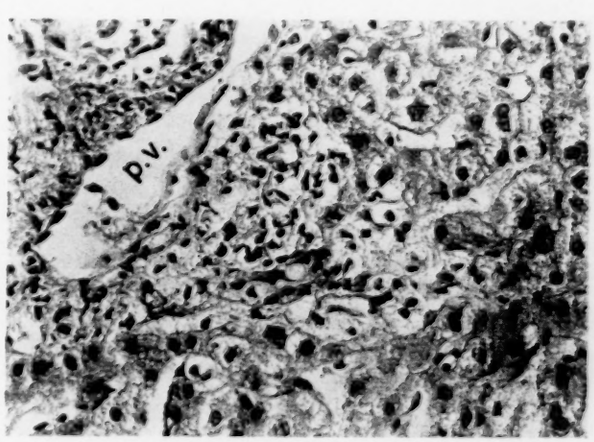


FIG. 6. Case 5, eighth day. Chlorpromazine jaundice, portal area. Feathery necrosis of periportal liver cells. The laminar plate has been destroyed by invasion of inflammatory cells from the portal space, but the feathery necrosis is occurring in a zone ahead of this infiltrate. Bile pigment was not apparent in this field, being confined to centrolobular zones. p.v. = portal vein. Hematoxylin and eosin, × 210.

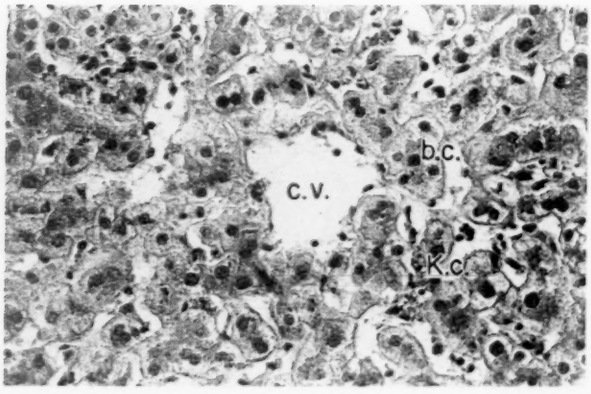


FIG. 7. Case 6, twelfth day. Chlorpromazine jaundice, centrolobular zone. Diffuse acidophilic cytoplasmic smudging of liver cells, with unicellular necroses, and sinusoidal infiltration by phagocytes. Note many double nucleated regenerating liver cells. b.c. = intracanalicular bile plug; K.c. = bile-filled Kupffer cell; c.v. = central vein. Hematoxylin and eosin, × 180.

and to 8.2 units six months after the onset, when the patient was dropped from observation. The serum cholesterol was 309 mg. per cent on the thirteenth day, and 267 mg. per cent on the eighty-second day, both values being normally esterified. The total lipids were 1.21 gm. per cent on the twelfth and seventeenth days, 2.12 gm. on the twentieth day, and 1.29 gm. per cent on the thirty-fifth day, the transitory rise corresponding in time with that of the serum bilirubin.

The serum colloid reactions were normal. The serum glutamic-pyruvic transaminase was 265 units on the twelfth day and fell to 90 units on the seventeenth day; then, concomitantly with the rise in serum bilirubin and total lipid, the values rose again to 204 units on the twentieth day, but were within normal limits when determined two weeks later and thereafter. Serum glutamic-oxaloacetic transaminases were not determined in this patient. Bromsulfalein retention at forty-five minutes was 8 per cent on the twenty-sixth day, 5 per cent on the thirty-ninth day and 4 per cent six weeks later.

Needle biopsy specimens of the liver were obtained on the twelfth, thirty-eighth, eighty-third and 186th days of illness. The initial biopsy specimen showed a moderate degree of centrolobular cholestasis, associated with a wide zone of degeneration of pericentral liver cells, many of which showed coagulative necrosis, and some feathery necrosis. (Fig. 7.) Focal necroses were small and infrequent. Large and multinucleated regenerating cells were present in moderate number. Phagocytes infiltrated the central sinusoids, which were widened, and many Kupffer cells contained bile and lipochrome pigments. The portal areas were moderately infiltrated with a mixed cellular exudate, containing a moderate number of eosinophilic granulocytes.

The second biopsy specimen, obtained on the thirty-eighth day, showed persisting cholestasis to lesser degree, although some of the canalicular bile plugs were larger and denser than before, and centrizonal coagulative necrosis of liver cells was now confined to a narrower pericentral zone involving fewer cells. Occasional small centrolobular focal necroses were also seen. Regenerating liver cells continued to be frequent in the centrolobular zones. Many lipochrome-filled Kupffer cells were seen in these zones, and some were in the portal spaces. Some steatosis of the centrolobular liver cells had appeared, perhaps associated with the patient's weight gain [*30*]. The portal cellular exudate had subsided considerably.

The third biopsy specimen, obtained on the eighty-third day, showed persistent centrolobular cholestasis of slight degree, with an improved appearance of the centrizonal liver cells. Vacuolated nuclei, irregularity in size of cells and their nuclei, and numerous double-nucleated liver cells were seen in the central zones. Steatosis persisted in many central areas. Lipochrome-filled Kupffer cells appeared more prominent. An occasional small focal necrosis was seen. The portal areas showed minimal but definite fibrosis not previously present and a slight persisting cellular infiltrate now entirely mononuclear.

The fourth biopsy specimen, obtained on the 186th day (six months), no longer showed bile canalicular plugging, although cytoplasmic bile pigment retention was present in the centrolobular cells which continued to show evidences of regeneration. Some steatosis, vacuolated nuclei, unicellular necroses and an occasional focal necrosis persisted. Phagocytes persisted in the sinusoids. The portal areas appeared normal.

Comment: Predominantly unicellular centrolobular liver cell necrosis in this case of chlorpromazine jaundice was associated with a rise in serum glutamic-pyruvic transaminase to 265 units. In this case, contrary to expectation, adrenocorticoid therapy was associated with a transient secondary rise in serum transaminase, bilirubin and lipid levels.

CASE 7. On the tenth day of chlorpromazine therapy, acute bronchitis, jaundice, abdominal discomfort, cramping pains in the legs and dizziness developed in a thirty-eight year old white man. The liver edge, palpable at the costal margin, was tender. The leukocyte differential count included 9 per cent eosinophils on the second day of illness, 8 per cent on the tenth day and 2 per cent on the thirteenth and twenty-fourth days.

The serum bilirubin on the second day of illness was 4.2 mg. per cent, of which 1.6 mg. was one-minute direct reacting. This fell gradually to normal within three weeks. The serum alkaline phosphatase was 17.3 Bodansky units on the ninth day of illness,

falling progressively to 7.1 units on the thirty-fifth day, but was still 8.9 units on the fifty-eighth day when the patient was dropped from observation. The serum cholesterol was 336 mg. per cent on the ninth day, 300 mg. on the thirty-fifth day and 267 mg. on the fifty-eighth day, all with normal esterification ratios. The serum albumin and globulin were normal. The cephalin cholesterol flocculation test was 1 plus in twenty-four hours on the ninth day, plus-minus on the thirteenth day and negative thereafter. The thymol turbidity remained normal. Bromsulfalein retention at forty-five minutes was 24 per cent on the tenth day, and 6 per cent on the twenty-fourth day. The serum glutamic-oxaloacetic and glutamic-pyruvic transaminases were 20 and 55 units, respectively, on the ninth day, and 18 and 19 units, respectively, on the twenty-fourth day.

A single biopsy specimen of the liver was obtained on the fifteenth day of illness. Bile stasis was evident in the centrolobular zones, both intracanalicularly and intracytoplasmically. Moderately severe degenerative changes and unicellular necroses were found in the liver cells of a narrow pericentral zone, while the lobules otherwise were nearly free of cell damage. Many large and multinucleated liver cells were present centrolobularly. The portal areas showed a moderate degree of mixed cellular infiltrate including an occasional eosinophil.

Comment: A transiently positive cephalin cholesterol flocculation test and transient elevation of serum glutamic-pyruvic transaminase, both of mild degree, were associated in this case of chlorpromazine jaundice with relatively mild indications of centrolobular liver cell necrosis in the biopsy specimen.

Case 8. After one month of chlorpromazine therapy, a sixty-nine year old white woman became ill with fever, epigastric pain, nausea and vomiting, constipation and dizziness. Dark urine was noted on the third day of illness, and icteric scleras on the tenth day. Fainting occurred on the seventh day. Moderate fever continued until the eighth day. When received on the medical service on the tenth day of illness, she had slight icterus of skin and scleras, and slight tenderness of the liver edge which was palpable 4 cm. below the costal margin. Enlargement of the liver was confirmed on roentgenographic visualization. Cholecystographic and intravenous cholangiographic studies were normal. The patient's nausea subsided on the twelfth day, and anorexia disappeared on the sixteenth day. On that day the icterus was fading, and the liver edge was smaller and less tender. Darker stools were noted on the nineteenth day, and the patient was asymptomatic thereafter.

An eosinophilia of 29 per cent was recorded on the fourth day of illness, falling to 18 per cent on the eleventh day and 6 per cent on the seventeenth day. Chamber eosinophil counts obtained during the eleventh to twenty-fifth days ranged from 900 down to 400 per cu. mm. A count on the forty-third day was still 330 per cu. mm.

The serum bilirubin on the eleventh day was 6.8 mg. per cent, of which 2.5 mg. was one-minute direct reacting. The serum total bilirubin fell to 1.8 mg. per cent on the eighteenth day, 1.3 mg. on the twenty-third day and was below 1 mg. per cent thereafter. The urine contained bile on the fourteenth day but not thereafter. Urobilinogen was not increased in the urine. The serum alkaline phosphatase was 31.5 Bodansky units on the fifteenth day, falling gradually thereafter to reach 7.3 units on the forty-third day, when the patient was dropped from observation. The serum total lipids rose from 0.7 gm. per cent on the eleventh day to 0.9 gm. per cent on the thirtieth day and 1.03 gm. per cent on the thirty-seventh day. The serum cholesterol varied from 192 to 300 mg. per cent, without apparent pattern. The esterified cholesterol was over 60 per cent of the total, except on the twenty-ninth and thirty-sixth days when 51 per cent and 57 per cent were recorded. The colloidal reactions of the serum were normal. Paper electrophoresis of the serum proteins on the eighteenth day revealed an increase in the beta globulin fraction to 19.7 per cent of 5.5 gm. total protein. Bromsulfalein retention at forty-five minutes was 3 per cent when determined on the twenty-third day. The serum glutamic-oxaloacetic transaminase was 90 units on the seventh day, rising to 110 units on the eleventh day and falling progressively thereafter to normal values by the twenty-fifth day. The serum glutamic-pyruvic transaminase was 155 units on the eighth day, rising to 170 units on the eleventh day, and falling progressively thereafter to 46 units on the twenty-fifth day and 18 units on the twenty-ninth day. (Fig. 5.)

Needle biopsy specimens of the liver were obtained on the eleventh and twenty-second days of illness. Centrolobular bile canalicular plugging was present in the initial biopsy. The central zones showed liver cell degenerative changes including unicellular feathery necrosis and bile necroses, and Kupffer cell proliferation as well as sinusoidal infiltration with granulocytes including eosinophils. Some of the Kupffer cells were filled with lipochrome. Large and multinucleated liver cells were present centrolobularly, and periportally as well. The portal areas were densely infiltrated with an extensive mixed cellular exudate containing many eosinophils, with destruction of the lobular limiting plates and widespread invasion of the periportal lobular zones, producing multicellular foci of feathery necrosis. (Fig. 8A.)

In the second biopsy specimen, obtained on the twenty-second day of illness, only occasional bile canalicular plugging was present, but in the centrolobular zones unicellular bile necroses were occa-

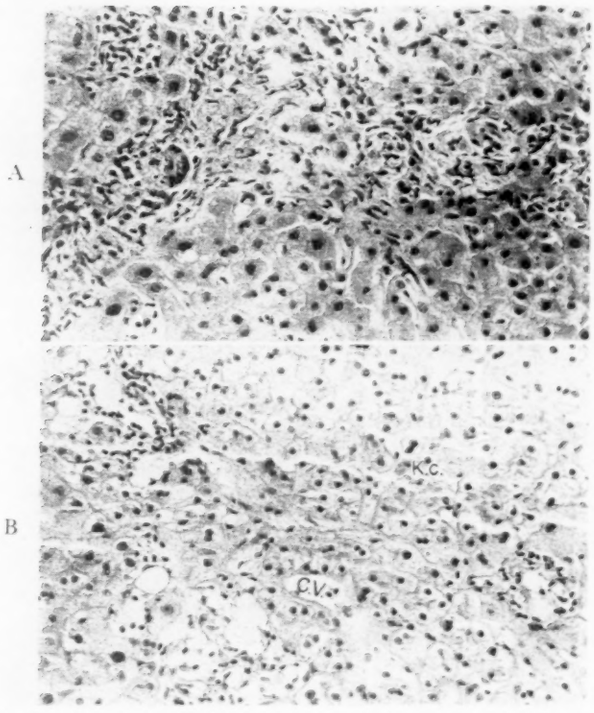


FIG. 8. A, Case 8, eleventh day. Chlorpromazine jaundice, portal area. Diffuse invasion of periportal lobular zone by mixed cellular exudate including eosinophilic granulocytes, with destruction of terminal plate and coagulative and feathery necrosis of liver cells. Hematoxylin and eosin, × 135. B, Case 8, twenty-second day. Chlorpromazine jaundice, centrolobular zone. A large focus of feathery, inflammatory and coagulative necrosis at left, adjacent to central vein (c.v.). A similar smaller focus is seen at right. Intracanalicular bile plugs are present but no longer prominent as they were on the eleventh day. Note large and double nucleated regenerating liver cells. K.c. = bile-filled Kupffer cell. Hematoxylin and eosin, × 135.

sionally found, and there were frequent multicellular mixed inflammatory and feathery necroses. (Fig. 8B.) A moderate number of lipochrome-filled Kupffer cells were present. Regenerating liver cells continued centrolobularly but were no longer prominent periportally. The portal areas showed much less inflammatory cell infiltration, and eosinophils were no longer prominent.

Comment: Periportal necrosis was prominent in the earlier biopsy specimen, but disappeared as the portal infiltrate subsided, whereas centrolobular liver cell necrosis increased. While both transaminases were elevated in the serum, the glutamic-pyruvic rose higher than the glutamic-oxaloacetic, following a parallel course (Fig. 5.) The beta rather than the gamma globulins were increased in the serum, and the total lipids rose during the period of observation.

CASE 9. On the twenty-first day of chlorpromazine therapy, fever, chills, chest pain and bronchial rales, vomiting and diarrhea developed in a thirty year old white man. There was a past history of alcoholism, but he had been confined to the hospital for psychiatric treatment during the immediately preceding three years. Examination revealed spider nevi of the upper chest and neck, a tender palpable liver edge extending 5 cm. below the costal margin, and a spastic sigmoid colon. Parenteral adrenocorticotrophin therapy was instituted during the first month of illness, resulting in prompt alleviation of symptoms and reduction of liver size, but without apparent effect on the clinical laboratory course. Cholecystographic roentgen examination eight months after the onset, performed because of persistent hyperphosphatasemia, revealed normal concentration and contraction.

The blood eosinophils were 13 per cent of the differential leukocyte count and totalled 1,080 per cu. mm. in a chamber count on the second day of illness. The chamber count was 1,620 per cu. mm. on the fourth day, but dropped rapidly thereafter to moderately elevated counts (240 to 450 per cu. mm.) which persisted through the next eight months of observation.

The serum bilirubin was 6.1 mg. per cent, of which 2.1 mg. was one-minute direct reacting, on the second day of illness. It rose progressively to a peak of 11.0 mg., of which 5.5 mg. was direct reacting, on the eighth day. Thereafter it dropped progressively to reach normal levels on the fiftieth day. Bile was found in the urine during the first two weeks of illness, but increases in urobilinogen were not observed. The serum alkaline phosphatase was 24.8 Bodansky units on the second day, and fluctuated between 21 and 33 units through the first three months of observation, failing to subside with subsidence of the icterus. When redetermined at five and one half months it was 35.8 units, and at eight months it was 40.0 units. The serum cholesterol was 246 mg. per cent on the tenth day of illness, rising progressively to reach 376 mg. per cent on the thirtieth day and falling with minor fluctuations thereafter to reach 239 mg. per cent on the eighty-eighth day. The total serum lipids rose from 715 mg. per cent at the onset to a peak of 951 mg. per cent two and one half months later. A transitory drop in serum albumin to 3.3 gm per cent was recorded on the eighth day of illness but was normal (4.3 gm.) one week later. Serum total globulins and gamma globulins were not increased, and the cephalin cholesterol flocculation and thymol turbidity tests were not abnormal during the illness, except for a single cephalin cholesterol flocculation determination of 4 plus in twenty-four hours on the forty-third day. Paper electrophoresis of the serum proteins performed two months after the onset yielded a normal pattern.

Serum cholesterol esterification was 30 per cent on the tenth day, 54 per cent on the fifteenth day and

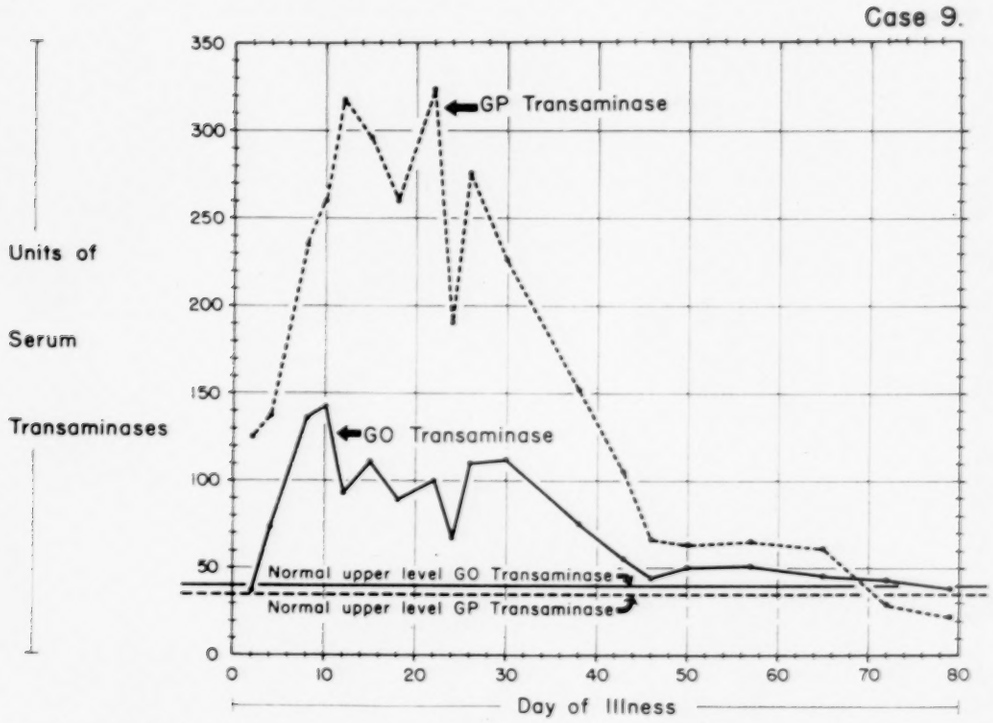


FIG. 9. Serum transaminase curves in a severe case of chlorpromazine jaundice (Case 9). Note that the two transaminase curves run parallel, but that the levels of glutamic-pyruvic transaminase exceed those of glutamic-oxaloacetic transaminase. Increased severity is reflected in higher and more prolonged elevations. (Compare with Figure 5.)

over 60 per cent thereafter. Bromsulfalein retention at forty-five minutes was 46 per cent on the fourth day of illness (but the one-minute direct reacting serum bilirubin was 1.6 mg. per cent on that day), 26 per cent on the forty-third day (serum direct bilirubin 0.4 mg.) and 25 per cent on the fifty-first day; the test was not repeated further because of production of venous thrombosis on two of these three occasions. A transitory prolongation of prothrombin time (15 seconds) was noted on the second day but not thereafter. The serum glutamic-oxaloacetic transaminase was 37 units on the second day, rose in daily increments to a peak of 142 units on the tenth day, and slowly subsided thereafter, not reaching normal values until two and one half months after the onset of illness. The serum glutamic-pyruvic transaminase was 125 units on the second day, rose progressively to a peak of 318 units on the twelfth day, and subsided slowly thereafter, reaching normal levels in the same week as the glutamic-oxaloacetic transaminase. (Fig. 9.)

Needle biopsy specimens of the liver were obtained on the fourth, twelfth, thirty-eighth and eighty-second days of the illness. The lobular structure of the liver was intact. In the initial biopsy the centrolobular zones showed cytoplasmic bile pigment retention in liver cells and bile canalicular plugging. The centrolobular liver cells showed numerous unicellular necroses, with occasional sinusoidal Councilman-like bodies and occasional mitotic figures. Multinucleation, although present both centrolobularly and periportally, was not prominent. Focal necroses were present throughout the lobules but predominantly centrolobularly. (Fig. 10A.) The inflammatory cells in these necrotic areas included many eosinophilic granulocytes. A rich cellular exudate densely filled the portal areas, and consisted of large and small mononuclear cells and numerous eosinophilic granulocytes. In some areas the portal exudate had broken the laminar plate and invaded periportally, resulting in necrosis of periportal liver cells. Bile ducts were infrequently found, and showed disorganization and necrosis of bile duct cells. The bile duct pictured (Fig. 10B) was the most nearly intact duct found in the entire biopsy specimen, which measured 2 cm. in length.

The second biopsy specimen, obtained on the twelfth day of illness, showed more prominent bile canalicular plugging and hepatocellular necrosis, but the portal exudate was less prominent and eosinophils were scanty. Bile necrosis of centrolobular liver cells was frequent, and many bile-filled Kupffer cells were seen. Large and multinucleated centrolobular liver cells were more abundant. Intact as well as dis-

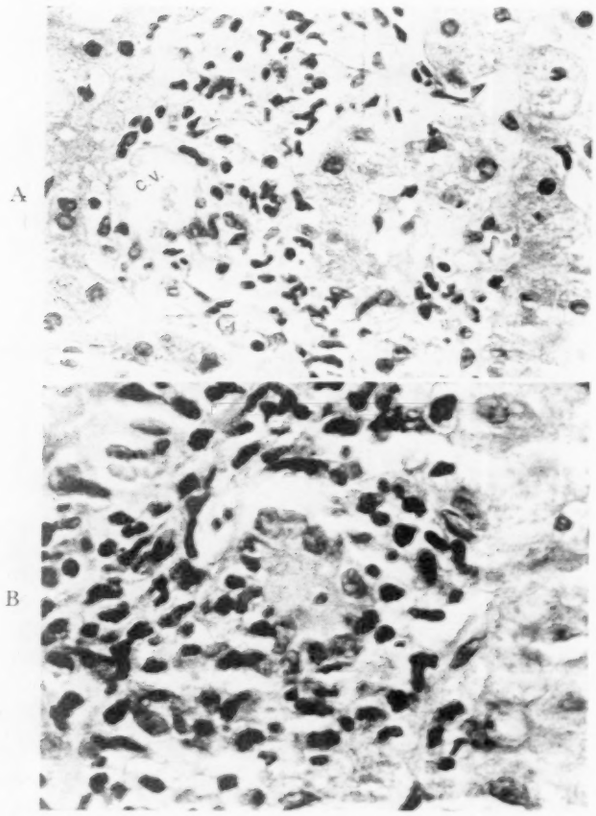


FIG. 10. A, Case 9, fourth day. Chlorpromazine jaundice, centrolobular zone. Large pericentral area of feathery necrosis infiltrated with monocytes and eosinophils predominantly, but lymphocytes, plasma cells and non-eosinophilic granulocytes are also seen. Lightly stained bile is present in liver cells and canaliculi. Liver cell regeneration is apparent. c.v. = central vein. Hematoxylin and eosin, × 325. B, Case 9, fourth day. Chlorpromazine jaundice, portal area. Small portion of a large portal space densely packed with a pleomorphic cellular exudate rich in eosinophilic granulocytes. Superficially resembling giant cell formation is an interlobular bile duct showing inflammatory necrosis of part of its wall. This was the most nearly intact bile duct in the entire biopsy specimen, which measured 2.0 cm. in length. Hematoxylin and eosin, × 490.

organized and regenerating bile ducts were present in portal areas.

In the third biopsy specimen, obtained on the thirty-eighth day, little bile canalicular plugging remained, and necrosis of centrolobular liver cells was minimal. Multicellular focal necroses remained throughout the lobules, however. Large and multinucleated regenerating liver cells were present centrolobularly and in lesser number periportally. Many lipochrome-filled Kupffer cells were seen centrolobularly and collected in some of the portal spaces. A moderate cellular exudate persisted in the portal areas, still containing some eosinophils as well as other varieties of phagocytes and fibroblasts, and there was some portal fibrosis not previously present. Intact as well as disorganized bile ducts were found, but regenerating bile ducts were no longer prominent.

A fourth biopsy specimen was obtained on the eighty-second day of illness. Small bile canalicular plugs still persisted in the centrolobular zones where mononuclear and polynuclear phagocytes infiltrated the sinusoids, and occasional lipochrome-filled Kupffer cells were seen. Focal necroses, both degenerative and inflammatory, were present in the centrolobular zones predominantly. Centrolobular liver cell regeneration was less prominent. The portal areas contained a mixed inflammatory infiltrate and some increase in collagen. The bile ducts continued moderately scanty, and many appeared disorganized.

The patient was restudied sixteen to eighteen months after the onset of illness. He was asymptomatic, still hospitalized, and engaging in regular moderate exercise. The liver edge was still palpable below the costal margin but was no longer tender. Chamber eosinophil counts were 300 and 325 per cu. mm. The serum proteins and paper electrophoretic fractions, gamma globulin, cephalin cholesterol and thymol turbidity tests were all normal. The serum lipids were 830 mg. per cent, the cholesterol 300 mg. per cent, normally esterified. The serum bilirubin and urine urobilinogen were normal, but the serum alkaline phosphatase was 40 Bodansky units, and the serum glutamic-oxaloacetic and glutamic-pyruvic transaminases were elevated, reading 66 and 68 units, respectively.

A fifth needle biopsy specimen of the liver was obtained on the 495th day since onset of the illness. Unicellular degenerative changes and regeneration still persisted among the liver cells of both pericentral and periportal areas. There was punctate and clumped bile pigment in the cytoplasm of pericentral liver cells but no plugging of canaliculi. Granulocytes were frequent in the sinusoids. There were many small inflammatory focal necroses, chiefly in periportal areas; these were characterized mainly by histiocytic infiltration but granulocytes were also seen. The portal spaces were not enlarged but showed an increase in collagen and a moderately dense infiltrate of histiocytes together with small mononuclear cells and granulocytes. Bile ducts were infrequent, the smaller ones difficultly recognizable because of irregularity of size and staining of the duct cell nuclei.

Comment: Clinically and histologically, this was the most severe case observed, one in which the highest serum transaminase levels were reached. (Fig. 9.) The unusual finding histologically was the involvement of interlobular bile ducts directly observable, as in Case 1. Despite clearing of the jaundice, and intact function of the biliary tree as indicated by normal roentgen visualization of the gallbladder, the patient has continued to show high serum alkaline

phosphatase levels as late as eighteen months after the onset.

COMMENTS

Eosinophilia. Peripheral blood eosinophilia was observed in seven of the nine patients, and may have been missed in the other two, inasmuch as detailed observations were not possible until the eleventh (Case 1) and eighteenth (Case 3) days of illness. The highest recorded values were 29 per cent of a differential leukocyte count (Case 8) and 1,620 per cu. mm. in a chamber count (Case 9). Eosinophilic infiltrations were found in the initial biopsy specimens of the liver of all but one (Case 3) of the nine patients. Peripheral blood eosinophilia probably occurs at least transiently in all cases of chlorpromazine jaundice, and is presumably a reflection of the eosinophilic infiltrations found in the liver.

Enlargement of the Liver. This was present grossly by palpation or by roentgen contrast visualization [*29*] in seven of the nine patients. Roentgen visualization was not obtained in the other two (Cases 5 and 7), in both of whom a liver edge was palpable at the costal margin. The spleen was not palpable in any of the nine patients, but splenic enlargement was noted on roentgen visualization in two (Cases 3 and 6).

Response to Adrenocorticoid Therapy. Adrenocorticoid therapy was employed in three patients (Cases 3, 6 and 9). In Case 9 symptomatic improvement and reduction in liver size followed, but the laboratory course and histologic appearance of the liver continued to be severe. Case 3 seemed to follow the normal course of resolution of the disease, and it is difficult to say whether that was influenced by therapy. In Case 6 the therapy was followed by increases in serum direct-reacting bilirubin, glutamic-pyruvic transaminase and total lipid.

Laboratory Evidences of Cholestasis. The serum total bilirubin was elevated in all nine patients, the peak values varying from 1.9 mg. per cent (Case 5) to 25.3 mg. per cent (Case 3). These peak values were attained as early as the second day of illness (Case 7) and as late as the twenty-eighth day (Case 3), with an average of 12.6 days. At these peak values the one-minute direct reacting fractions ranged from 21 per cent (Case 5) to 53 per cent (Case 1) of the serum total bilirubin. Icterus persisted (above 1 mg. per cent total bilirubin) from seven days (Case 5) to over 115 days (Case 3).

The serum alkaline phosphatase reached its peak value at the time of the peak serum bilirubin, or within eleven days thereafter. However, increased levels persisted longer, varying from twenty-two days (Case 5) to over eighteen months (Cases 3 and 9). The peak values ranged from 7.6 (Case 5) to 98 (Case 1) Bodansky units.

Serial determinations of the total lipids were available in four patients. Rises were noted in all; the highest value was 2.12 gm. per cent (Case 6) or 1.77 times the lowest value subsequently determined in this patient. Serial serum cholesterol determinations were available in all nine patients, increases from basal levels (revealed in retrospect) occurring in all. The highest serum cholesterol observed was 720 mg. per cent (Case 1) or 2.74 times the lowest value subsequently recorded in this patient. All but one of the other eight patients had peak cholesterol values over 300 mg. per cent, whereas their basal levels (lowest values recorded) ranged from 143 to 267 mg. per cent. The peak serum cholesterol values were reached within thirty-eight days of the onset in all but one case; three of the four peak serum total lipid values were also reached within this time period. In all patients the peak serum lipid and cholesterol values were reached later than the peak serum bilirubin values, and in all but one case later than the peak serum alkaline phosphatase values.

Laboratory Evidences of Liver Cell Damage. Elevations of the serum glutamic-pyruvic transaminases were found in all of the six patients in whom this determination was made. The highest value recorded was 318 units (Case 9). The serum glutamic-oxaloacetic transaminase was elevated in four of the six patients in whom it was determined, but remained within normal limits in the two patients (Cases 5 and 7) showing the least rise in glutamic-pyruvic transaminase. The highest recorded value of serum glutamic-oxaloacetic transaminase was 142 units (Case 9). The curves of serial determinations of the two serum transaminases were parallel in each patient, the glutamic-pyruvic transaminase values being higher. (Figs. 5 and 9.) The peak serum transaminase values occurred within nineteen days of the onset of illness.

Rises in the serum transaminases have been related to tissue necrosis, and in a parallel study by Zelman, Wang and Appelhanz [*31*] were found to correlate grossly with histologic evidences of liver cell necrosis in 143 needle biopsy

specimens of the liver. Eleven of the twenty-six biopsy specimens described in this report were included in that study. There appears to be no reason why elevations of the serum transaminases in chlorpromazine jaundice should not be considered to reflect liver cell necrosis just as much as they do in other diseases of the liver. The relatively modest increases in serum transaminases in this disease as compared with viral hepatitis are consistent with the lesser amount of liver cell necrosis found histologically despite comparable hyperbilirubinemia.

There were additional laboratory evidences of liver cell damage. Transitory depressions of serum cholesterol esterification were observed in four patients, the lowest being 30 per cent (Case 9). Depressed bromsulfalein clearances (less than 95 per cent in forty-five minutes, of an intravenous dose of 5 mg. per kg.) not attributable to cholestasis (less than 1 mg. per cent one-minute direct-reacting serum bilirubin) were seen in six cases, the maximum retention recorded being 26 per cent in forty-five minutes (Case 9). Disturbances in one or more of the colloidal reactions of the serum occurred in six of the nine patients; these were usually but not always transient. Transient minor prolongations of the one-stage Quick prothrombin time occurred in three patients.

The relative infrequency of positive colloidal reactions of the serum in chlorpromazine jaundice has been ascribed to inhibition of these reactions produced by cholestasis [*32*]. Also, it must be considered that in viral hepatitis the infecting virus may itself contribute to the positive colloidal reactions found in that disease, either by its presence in the blood or by antibody production and other reactions it invokes in the host. Chlorpromazine jaundice appears to represent a non-infectious disease, consisting of an allergic reaction to the drug or its metabolic products, a concept which has been adequately presented by others [*33*].

Histologic Evidences of Cholestasis. In the earliest biopsy specimens, cholestasis was apparent only as granules of bile pigment within cytoplasm of the centrolobular liver cells, aligned along the bile canaliculi, and found also within the canaliculi. In later biopsy specimens, twig-like branching casts of dense, homogenous bile pigment outlined the canaliculi. Still later, the canaliculi were distended and contained large, deeply stained, globular masses of pigment. These gradually faded and grew smaller as the patients recovered. Small intracanalicular masses and casts often persisted for prolonged periods after clinical recovery. In none of the patients were evidences of cholestasis found anywhere but in the centrolobular zones. The two patients who had necrosis of interlobular bile ducts showed no bile pigment within those ducts.

Portal Infiltration and Fibrosis. The portal infiltrate was a mixed one, consisting of large and small mononuclear cells, granulocytes and eosinophils. A similar mixed cellular infiltrate invaded the sinusoids and the intralobular focal necroses. In some of the later biopsy specimens, only a residual infiltration of lymphocytes was found in the portal spaces.

Some degree of portal fibrosis followed resolution of the portal infiltrate in five patients (Cases 1, 2, 3, 6 and 9). This was generally of mild degree, and proved transient in two (Cases 1 and 6). It might have proved transient in all had they been followed up sufficiently. It was found as early as the twenty-fifth day of illness (Case 1) and as late as sixteen months after the onset (Case 9); in the other three patients it was noted on the thirty-eighth, eighty-first and 207th days.

Histologic Evidences of Liver Necrosis. Unicellular liver cell necroses were found in significant numbers in the centrolobular zones in all nine patients. All but one (Case 7) also showed multicellular focal necroses in these zones. Two patients (Cases 1 and 9) had multicellular focal necroses also in the periportal zones. All but three (Cases 3, 6 and 7) of the patients showed periportal invasion of the lobules by the portal exudate, with necrosis of periportal liver cells. Lipochrome-engorged Kupffer cells were prominent in all but one patient (Case 7).

In no case did the extent of liver cell necrosis approach that seen in viral hepatitis other than in its convalescent stage, but it was usually more persistent. There seemed to be a rough correspondence of the amount of liver cell necrosis with the height of the serum transaminases, particularly the serum glutamic-pyruvic transaminase.

With the exception of the foci of feathery necrosis (to be discussed subsequently) the forms of liver cell necrosis were those commonly seen in viral hepatitis, including the eosinophilic Councilman-like bodies produced by shedding of dying liver cells from the liver cell plate into the sinusoids, a phenomenon which is sometimes described as pathognomonic of viral hepatitis, although I have seen it in other forms of liver

necrosis, particularly toxic hepatitis and alcoholic necrosis, but never, of course, in such numbers as found in viral hepatitis. The Kupffer cell reactions were also similar. The differences from viral hepatitis were of degree rather than of kind. The limitation to the centrolobular zones may also represent a quantitative difference, since in viral hepatitis the process is usually most severe in those zones. The sinusoidal and portal infiltrates differed from those of viral hepatitis, which are predominantly mononuclear.

Possibly the failure of some authors to stress the finding of liver cell necrosis in chlorpromazine jaundice has been due to this significantly lesser involvement than found in viral hepatitis, which, consciously or unconsciously, serves the histopathologist of biopsy specimens of the liver as a standard. In addition, pathologists not experienced with aspiration biopsy specimens of liver tissue will overlook centrolobular necroses, since these occur commonly in necropsy tissue as an agonal or postmortem change [*34*], and to some extent also in surgically biopsied liver tissue [*35*].

Regeneration of liver cells was evident in the centrolobular zones of all nine patients, usually in the form of large and multinucleated cells with multiple nucleoli, but in two patients (Cases 1 and 9) mitotic figures were frequent as well. Liver cell regeneration was also noticeable in the periportal zones in three patients (Cases 4, 8 and 9).

Necrosis of interlobular bile ducts, and their regeneration, occurred in two patients (Cases 1 and 9), these being the two most severe cases of the series. It is suggested that a destructive process ordinarily limited to the intralobular radicals (cholangioles) of the biliary tree in these two severe cases extended to involve also the septal ducts, making these instances of interlobular cholangitis as well as "cholangiolitis."

Feathery Necrosis. Feathery necrosis of liver cells was seen centrolobularly in six (Cases 1, 2, 5, 6, 8 and 9) of the nine patients, and periportally in three (Cases 1, 5 and 8). This phenomenon is reported to occur only in cholestasis, whether intrahepatic or extrahepatic. Since this form of necrosis plays so large a role in chlorpromazine jaundice, and has apparently been unrecognized in some reported cases, it may be well to describe it further.

Writing of extrahepatic cholestasis, Weisbrod et al. [*36*] reported: "In the cases of longer standing, groups of liver cells show a rather striking degenerative change manifested by flattening of the cells, which assume a radial arrangement. There is pallor of staining permitting the ordinarily inconspicuous reticulum to stand out with unusual prominence. The nuclei are shrunken and pyknotic; necrosis of the usual type does not occur and there is only a sprinkling of lymphocytes at the periphery of this lesion. The radial pattern and the reticulum framework give the lesion a 'feathery' appearance. Ultimately there is disruption of the minute bile passages included and small pools or 'lakes' of bile appear in the centers of the foci. These 'bile lakes' are highly characteristic and have only been encountered in the presence of severe obstruction."

According to Popper and Schaffner [*37*]: "In prolonged intrahepatic or extrahepatic cholestasis, hepatic cells laden with bile pigment or near bile plugs have a rarified cytoplasm, in which a fine brown pigmented protoplasmic network is found. This has been called 'feathery degeneration.' The nucleus is central and pyknotic. The changes involve scattered cells, mainly in the center of the lobule, and groups of cells on the periphery of the lobule in bile infarcts.

"In either scattered or aggregated cells with feathery degeneration, the nuclear staining disappears, and the cytoplasm of the swollen cells contains a bile-imbibed protein network (reticular biliary necrosis), for instance, as seen in bile infarcts. As isolated cells with feathery necrosis disappear and bile canaliculi rupture, the adjacent bile plugs are left outside the biliary passage, and the term 'bile lake' is applied. The cells surrounding the small necrotic area are not significantly altered."

No bile lakes were seen in the areas of feathery necrosis found among my nine cases. Bile staining was present in those located centrolobularly but not in the periportal foci. The latter were smaller, and related to intralobular extensions of the portal infiltrate, occurring in advance of the actual extensions. (Fig. 6.) In such cholangiolitic portal infiltrates, Popper [*38*] has noted droplets around bile ducts which give the same sudanophilic reaction as the canalicular bile plugs, suggesting periductal regurgitation of bile.

The larger foci of feathery necrosis were scantily infiltrated by the same mixed cellular infiltrate rich in eosinophils which existed in the portal spaces. There was a gradual transition

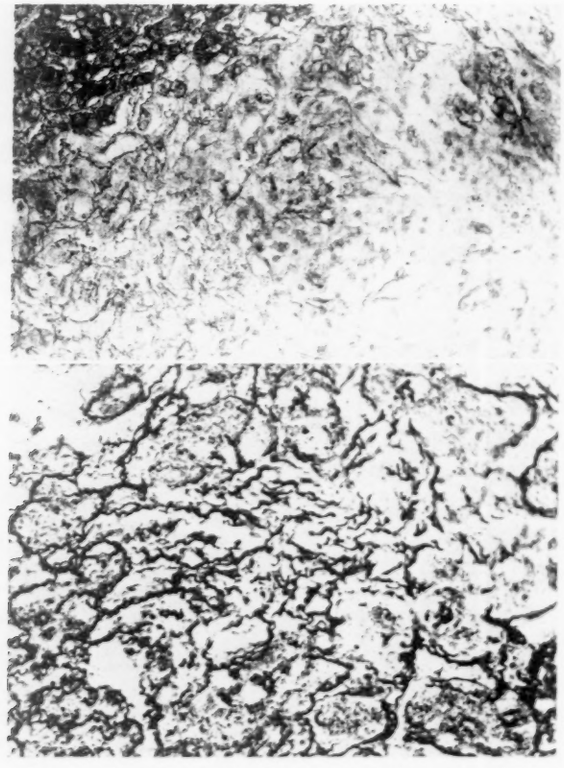


FIG. 11. A, Case 2, eighty-first day. Reticulum stain of transitional zone at edge of necrotic area pictured in Figure 2A. There is a gradual transition from intact reticulum at left above to its complete disappearance at right below. Gridley's reticulum stain, × 135. B, Case 2, eighty-first day. Chlorpromazine jaundice, centrolobular zone. Condensation of reticulum is seen in an area of focal necrosis. Gridley's reticulum stain, × 410.

(Fig. 2B) from unaffected liver cells at the periphery of the larger lesions. There was no indication of collapse of these foci, an observation that seems to have led some authors [*28,36*] to conclude that the reticular framework has been preserved. Reticulum stains of the large centrolobular focus of feathery necrosis in Case 2 showed destruction of that framework, however. (Fig. 11A.) There was no condensation of the disintegrating reticulum fibers, and no indication otherwise of collapse of this or other areas of feathery necrosis in these cases. This finding is in distinct contrast to the condensation of reticulum fibers found in non-feathery focal necroses (Fig. 11B), noted also by Bartholomew et al. [*27*].

Popper has referred to the intracellular reticulated appearance of the degenerating liver cells of these foci of feathery necrosis as "a bile imbibed protein network (reticular biliary necrosis)," which appears to describe the phenomenon adequately. Presumably bile or one of its constituents causes precipitation of a thread-like network of protoplasmic components at the same time that other cell contents appear to undergo dissolution. The nuclei are only quantitatively more resistant than the cytoplasm, as seen in the transitional zones (Fig. 2B), where they persist longer but finally disappear in the central portions. The extracellular reticular fibers appear to suffer the same fate. (Fig. 11A.)

Of the reported fatalities following chlorpromazine therapy, two are sufficiently well documented to warrant the diagnosis of fatal chlorpromazine hepatitis (allergic cholangiolitis). These have been mentioned earlier [*18,28*]. The first case at autopsy showed "hepatomegaly with acute aseptic necrosis of the liver," indicating necrosis without collapse. The second case also showed diffuse centrolobular non-inflammatory necrosis "with preservation of the supporting reticulum," although actual use of reticulum stains is not mentioned. These descriptions and the photomicrographs published with the second case report suggest that the liver necrosis in these fatal cases took the form of centrolobular bile infarcts or "feathery necrosis." It would seem that the bile lakes which occur in large periportal infarcts are not seen centrolobularly, perhaps because spilling of bile from the rupture of canaliculi is insufficient to form such lakes, in contrast to the bile losses after destruction of the larger septal bile ducts.

Pathogenesis of Liver Cell Necrosis in Chlorpromazine Jaundice. The visible evidences of interlobular bile duct destruction in the two most severe cases of this series lead to the assumption of similar damage to the generally invisible intralobular cholangioles. Damage to these structures has long been held to account for the phenomenon of intralobular cholestasis, a concept embodied in the term "cholangiolitis" [*39*]. Cholestasis appears centrolobularly regardless of the site of actual interference with bile flow [*40*].

In electron microscopic studies of liver cell structure [*41*], bile canaliculi are seen to widen during bile stasis, and to become surrounded by a rich deposit of bile pigment. When pigment deposition exceeds a certain mass the adjacent liver cells become necrotic, and this is associated with or preceded by regurgitation of bile into the blood stream. Popper [*42*] describes a "pericholangiolitis" occurring as a response to regurgitation of bile from damaged cholangioles, or following established extrahepatic biliary obstruction, and resulting in liver cell damage.

The cytotoxic action of bile is well known [*43*]. It is both bacteriolytic and hemolytic, and has a detergent action which denatures proteins. Addition of bile to liver tissue *in vitro* causes grave disturbances in intracellular functions, especially respiration [*44*]. We have ourselves produced the histologic appearance of feathery necrosis of liver cells simply by dipping one end of fresh biopsy specimens of the liver into gallbladder bile obtained at autopsy [*45*].

After experimental obstruction of extrahepatic bile ducts, liver cell necrosis is a constant and early effect, being found within an hour after obstruction, and followed by further necrosis and atrophy as well as regeneration of liver cells [*46*]. While in the rat the necrotic regions are periportal, in the cat necrosis develops midzonally or centrolobularly when its common bile duct is obstructed, and some animals show focal necroses which come and go in variable locations within the lobules. Liver cell necrosis develops in one parabiotic animal when the common bile duct of its partner is ligated, so the effect is not dependent on hydromechanics [*47*].

However, while the action of retained bile may account for liver cell necrosis which appears as focal necroses, feathery necroses and bile necroses or bile infarcts, lesions which may be seen in uncomplicated extrahepatic biliary obstruction, an additional factor of primary hepatic cell damage in chlorpromazine jaundice must be postulated to account for the evidences of unicellular necroses seen centrolobularly which mimic, although mildly, the histopathology seen in viral hepatitis. Such cell damage is presumably a direct result of the reaction of the liver cells to the drug or its metabolic products in susceptible individuals. The precise mechanism remains to be elucidated. The appearance of serum transaminase elevations prior to jaundice in patients taking chlorpromazine [*25*] (as occurs also in viral hepatitis [*48*]) may further signify independent hepatocellular damage.

A third form of liver cell necrosis in chlorpromazine jaundice is directly attributable to the inflammatory cellular infiltration in the portal spaces, which in six of the nine patients broke through the terminal liver cell plates to invade the periportal lobular zones. Such invasions are seen to disrupt liver cell plates, isolating and destroying cells. This phenomenon is seen with exuberant portal inflammatory infiltrates of various causes [*49*].

SUMMARY

Nine patients with chlorpromazine jaundice were studied for periods varying from forty-three days (Case 8) to over three years (Case 1). Twenty-six needle biopsy specimens of the liver were obtained in these nine patients, varying from one (Case 7) to five (Case 9) biopsy specimens per patient. The clinical, laboratory and histopathologic features are described in detail in case protocols.

Although much less prominent than in viral hepatitis, necrosis of liver cells is found in chlorpromazine jaundice, notably in the centrolobular zones adjacent to the evidences of cholestasis, and frequently also in periportal intralobular extensions of the portal exudate. It is accompanied and followed by intralobular liver cell regeneration, characterized both by multinucleation and by mitosis. The necrosis of liver cells is reflected in rises in serum glutamic-pyruvic transaminase, and to lesser degree in serum glutamic-oxaloacetic transaminase. The findings suggest that necrosis of liver cells (hepatitis) may play a more important role in the causation of chlorpromazine jaundice than is generally recognized.

The disease histopathologically is of prolonged duration compared with the transitory symptomatology. This duration is reflected in the laboratory measurements, particularly in the serum alkaline phosphatase, and often in persisting eosinophilia. There was no evidence in these cases of the development of permanent residual damage or fibrosis in the liver, although a transient portal fibrosis was observed to follow resolution of the portal infiltrations.

Disorganization and necrosis of interlobular bile ducts, followed by their regeneration, occurred in the two most severe cases of this series, suggesting extension of a destructive process ordinarily limited to the intralobular cholangioles.

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A Familial Study in Idiopathic Hemochromatosis*

T. H. Bothwell, m.d., I. Cohen, m.b., O. L. Abrahams, b.sc. *and* S. M. Perold, b.sc.

Johannesburg, South Africa

It is generally believed that the clinical manifestations of idiopathic hemochromatosis reflect the tissue damage caused by excessive iron in the body [*1*]. Thus the liver, which is the chief reservoir, becomes cirrhotic and the heavy pancreatic deposits lead to diabetes in about 80 per cent of subjects. In addition the skin becomes pigmented. Cardiac involvement is not uncommon.

Since iron overload occupies the central role in the pathogenesis of the disease, rational therapy is directed towards the removal of this iron by repeated venesections [*2,3*]. On this regimen iron is mobilised from stores to satisfy the increased needs of the erythroid marrow. Such therapy has caused amelioration of symptoms and it seems probable that it will improve the prognosis of patients with the disease. However, the degree of improvement must depend on the amount of damage to the organ that has occurred prior to the start of treatment. The ideal subject for therapy would therefore be someone in whom excessive iron stores had not been present in sufficient quantities for a long enough period to cause irreversible tissue damage. Unfortunately these cases are difficult to diagnose as clinical manifestations are evident only when the iron has already led to considerable pathologic changes. Since, however, there is growing evidence that idiopathic hemochromatosis may be a familial inborn error of metabolism [*1*] it is possible to detect a proportion of such cases by investigating relatives of patients with overt disease. Although reported examples of the fully developed clinical disease in relatives have been few, it has been shown that about 20 per cent have elevated serum iron levels [*1,4*].

The present paper records the results of such a survey. These findings have some bearing on the pathogenesis of the condition and also underline the practical importance of detailed familial studies in idiopathic hemochromatosis.

METHODS

Fifty-two immediate relatives (i.e., parents, siblings and children) of six patients with idiopathic hemochromatosis were investigated. The six patients were all subjects in whom the disease had been confirmed histologically. In five it was proved at autopsy and in one by liver biopsy.

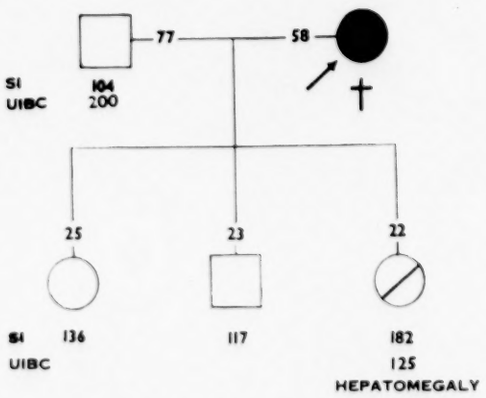
Each of the relatives was examined clinically, and fasting serum iron estimations were made by the method of Bothwell and Mallett [*5*] in all except five young children. In this laboratory the average normal figures for serum iron are 114 μg. /100 ml. for males and 104 μg./100 ml. for females. Although values above 150 μg./100 ml. have been found in some healthy subjects they have not been constantly raised on repeated testing. In the present study results above 150 μg./100 ml. were therefore regarded as abnormal only when present on two or more successive occasions. In addition the unsaturated iron-binding capacity was estimated in about half the subjects, using the technic of Rath and Finch [*6*]. When possible, liver biopsies were performed in relatives showing persistently raised serum iron levels. Sections of these biopsy specimens were stained with hematoxylin and eosin, and with Prussian blue by Dry's method [*7*].

RESULTS

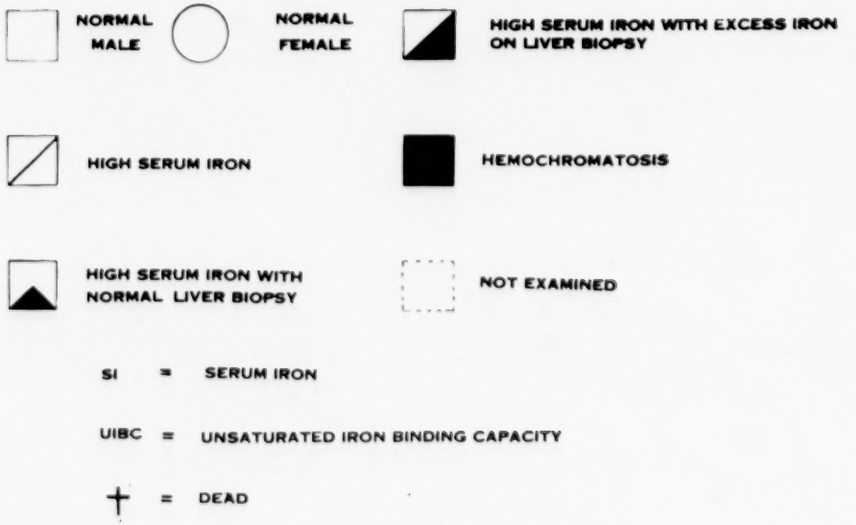
The salient clinical features of propositi and affected relatives are recorded in the family reports which follow. These reports also include the relevant biochemical abnormalities and, in most instances, the results of liver biopsy. (Figs. 1 and 2.)

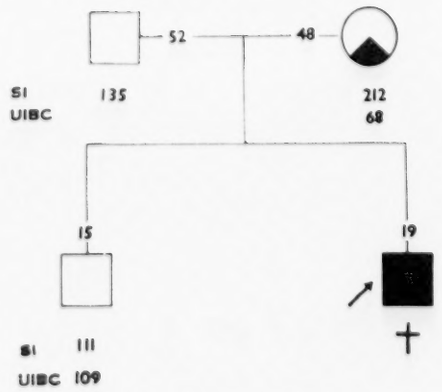
Family A. The propositus was a woman who had been followed for several years as an established case of hemochromatosis prior to her death at the age of fifty-eight years. She finally died following a hematemesis.

* From the Department of Medicine and the Department of Pathology and Microbiology, University of the Witwatersrand, Medical School, Johannesburg, South Africa.

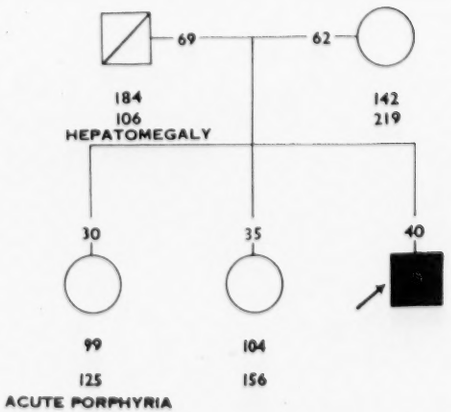


FAMILY A

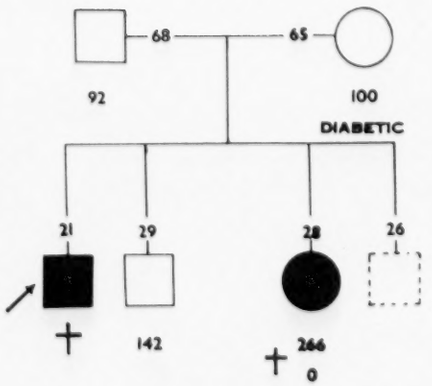




FAMILY B



FAMILY C



FAMILY D

FIG. 1 Pedigrees of four families.

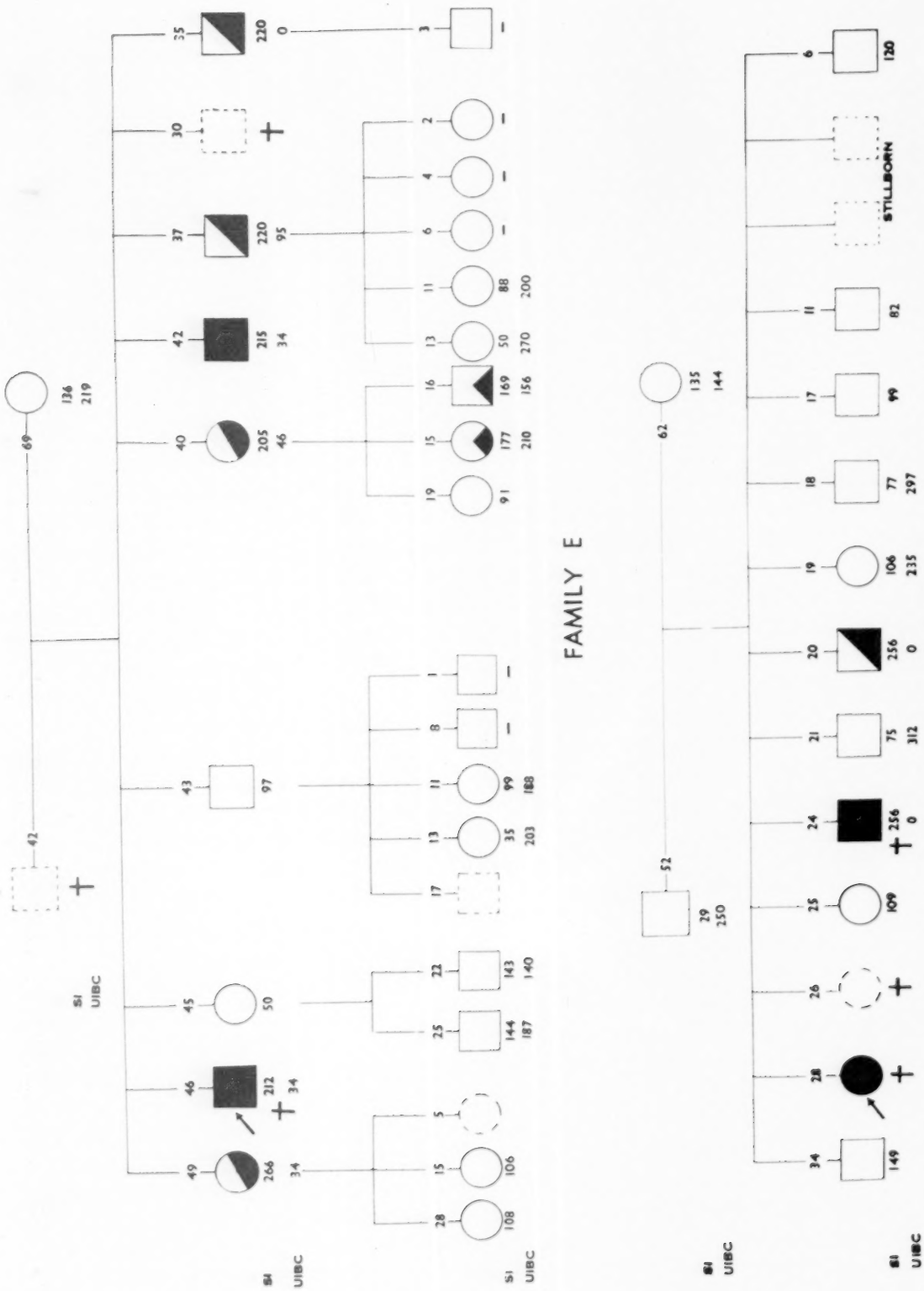


FIG. 2. Pedigree of two families.

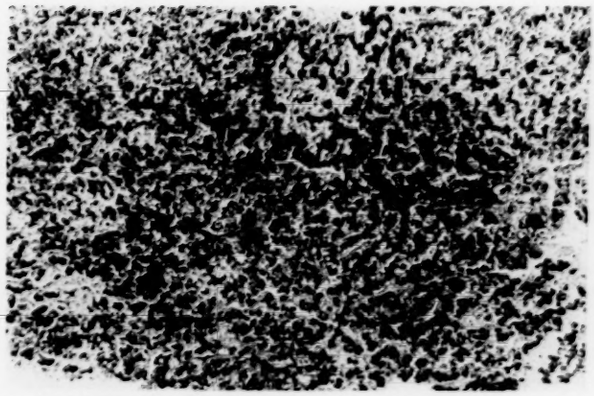


FIG. 3. Family D. Liver biopsy specimen from a twenty-eight year old woman. Hemosiderin granules are present in parenchymal cells. The portal tracts (not shown in figure) show round cell infiltration and slightly increased fibrosis. Perl's stain. Original magnification × 120.

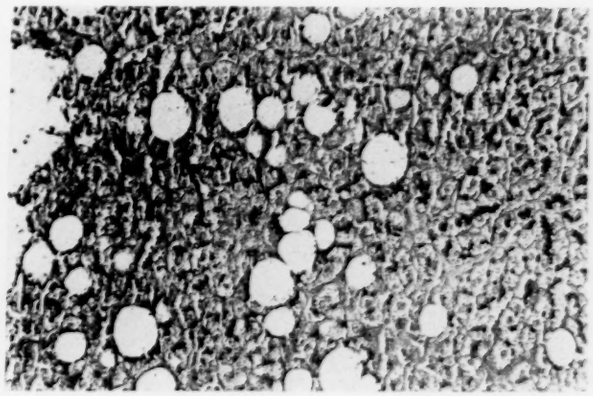


FIG. 4. Family E. Liver biopsy specimen from a forty-nine year old woman. There is marked peripheral fatty change and fine hemosiderin granules are present in parenchymal cells. The portal tracts show no increased fibrosis. Perl's stain. Original magnification × 240.

The husband and three children were examined. The only abnormalities detected were in a daughter, aged twenty-two years, who had a firm two-finger hepatomegaly, a raised serum iron level and a reduced unsaturated iron-binding capacity. No pigmentation of the skin was noted. Menstruation was normal. She refused further investigation.

Family B. The propositus was a young man in whom diabetes developed. He subsequently died in cardiac failure at the age of nineteen years.

The parents and an only brother were examined. All appeared clinically normal but the mother, who was forty-eight years old, had a serum iron level above 200 μg./100 ml. on three separate occasions over a period of eight months. A hysterectomy had been performed three years previously for menorrhagia of several years' duration. Liver function tests were normal as was the blood count (hemoglobin 14.5 gm./100 ml.). Finally a liver biopsy was performed. No abnormalities in the liver were found. Venesections were then started at three weekly intervals. After approximately 1,200 mg. iron had been removed in this way the hemoglobin level was 12.5 gm./100 ml. and the serum iron level was 35 μg./100 ml. At this stage venesections were discontinued.

Family C. The propositus was a forty year old man with diabetes, pigmentation of the skin and testicular atrophy. A diagnosis of hemochromatosis had been established by liver biopsy several years previously. At the time his relatives were studied about 35 gm. iron had already been removed from the patient by phlebotomy.

The parents and two sisters were examined. One sister was known to have acute intermittent porphyria but showed no evidence of iron excess. The only other abnormalities were found in the father who had a firm hepatomegaly and a high serum iron level. In view of his age and apparent good health no further tests were carried out.

Family D. The propositus was a young man, aged twenty-one years, who succumbed to the cardiac complications of the disease. Full details of this patient, including radioiron data, have been recorded elsewhere [*8,9*].

The patient's parents and two siblings were examined. The brother was normal but the sister showed classic clinical features of the disease with pigmentation of the skin, endocrine changes and cardiac signs. The diagnosis was confirmed by liver biopsy. (Fig. 3.) In spite of energetic therapy she died at the age of twenty-eight years in gross congestive failure. (The clinical features of this patient have also been described previously [*10*].) The father appeared normal but the mother was found to be a diabetic of several years standing whose diabetes was adequately controlled on 20 units of protamine zinc insulin daily. In addition she had a two-finger hepatomegaly. In view of these findings a biopsy specimen of the liver was obtained, in spite of the fact that the serum iron level was persistently normal. Histologically the sections appeared normal with no evidence of excessive iron deposits.

Family E. The propositus was a forty-six year old man in whom cardiac failure developed. In addition there was pigmentation of the skin and a three-finger hepatomegaly, but no diabetes. The diagnosis of idiopathic hemochromatosis was supported by skin biopsy findings. He died suddenly several months after the onset of symptoms, and at autopsy showed the typical features of the disease.

The mother was examined and appeared normal. The father was reported to have died at the age of forty-two years from "acute heart failure" but unfortunately no further details were available. In

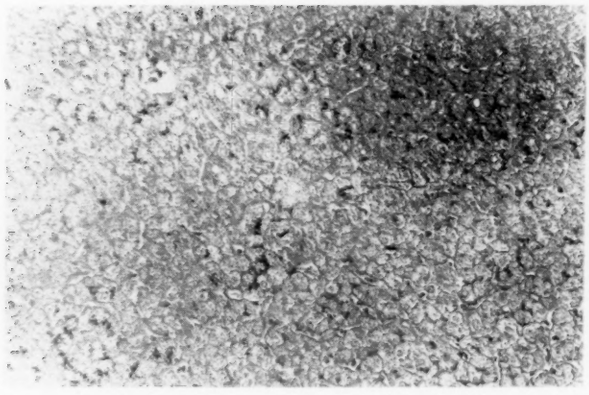


FIG. 5. Family E. Liver biopsy specimen from a forty year old woman. Scattered foci of liver cells contain fine hemosiderin granules. The histology is otherwise normal. Perl's stain. Original magnification × 240.

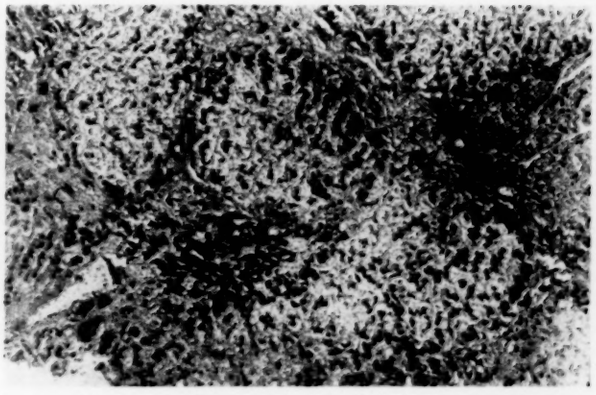


FIG. 6. Family E. Liver biopsy specimen from a forty-two year old man. Coarse hemosiderin granules are present in the parenchymal cells and also in the Kupffer cells and portal tracts. There is well marked fibrosis of the portal tracts with linkage of adjacent tracts. Areas of nodular regeneration are present. Perl's stain. Original magnification × 150.

addition a brother had been killed in an accident at the age of thirty. All the other seven siblings were investigated. Of these only two, a brother and sister, were completely normal. All the remaining siblings showed raised serum iron levels, reduced unsaturated iron-binding capacities and abnormal findings on liver biopsy.

The eldest was a forty-nine year old woman, with three children, the youngest of whom was eight years old. A hysterectomy had subsequently been carried out because of menorrhagia. On examination there was a suggestion of pigmentation of the skin and a one-finger hepatomegaly. The liver biopsy showed scattered deposits of hemosiderin confined to parenchymal cells and well marked fatty infiltration. (Fig. 4.) There was no increased fibrosis of the portal tract. Liver function tests and a glucose tolerance curve were within normal limits.

The other affected sister was a forty year old woman with three adolescent children, who was clinically normal. In view of the serum iron findings a biopsy specimen of the liver was obtained. Fine granules of hemosiderin were present in parenchymal cells but the histologic findings were otherwise normal. (Fig. 5.)

The eldest affected brother was forty-two years old. He gave a history of having suffered from dyspnea on effort for the previous six months. On examination he was found to be in mild congestive failure with cardiomegaly and a gallop rhythm. There was generalised slaty grey pigmentation and a three-finger firm hepatomegaly. The glucose tolerance was normal. A biopsy specimen of the liver showed the typical features of idiopathic hemochromatosis with a well marked monolobular cirrhosis and extensive iron deposits. (Fig. 6.)

Another brother, aged thirty-seven years, gave a history of an excessive alcohol intake but otherwise appeared to be normal. A liver biopsy showed finely dispersed hemosiderin throughout the liver cells but there was no increase in fibrous tissue. (Fig. 7.)

The last affected brother was thirty-five years old, with no subjective complaints. On examination there was some generalised pigmentation with a one-finger hepatomegaly. Liver biopsy showed massive iron deposits with early portal fibrosis. (Fig. 8.)

Seventeen members of the third generation of the family were examined. All were clinically normal but a daughter and son of an affected female, aged fifteen and sixteen years, respectively, showed serum iron levels persistently between 150 and 200 μg./100 ml. Sections from liver biopsy specimens were, however, quite normal. The daughter was subsequently venesected weekly until the hemoglobin level had fallen to 9.0 gm./100 ml. At this stage approximately 1500 mg. iron had been removed.

Family F. The propositus, a yound woman who died at the age of twenty-eight in cardiac failure, has been fully described elsewhere [*11*]. Both parents appeared to be healthy although the mother, who had given birth to fourteen full term infants, complained of menorrhagia. Her serum iron level was only 29 μg./100 ml. but she did not appear to be anemic. A possibly significant point in the family history was the fact that a brother of the mother had died from diabetes at the age of sixty-two years.

Two of the patients' siblings were stillborn and a sister had died at the age of twenty-six years from a "bleeding disorder." The remaining ten siblings were all examined. One brother, aged twenty-four years, was found to be under treatment elsewhere for fully developed hemochromatosis. The salient features were pigmentation of the skin, diabetes and pituitary infantilism. A biopsy specimen of the liver showed the characteristic features of the disease. (Fig. 9.) He subsequently died in heart failure. Another brother, aged twenty years, in apparently good health, showed

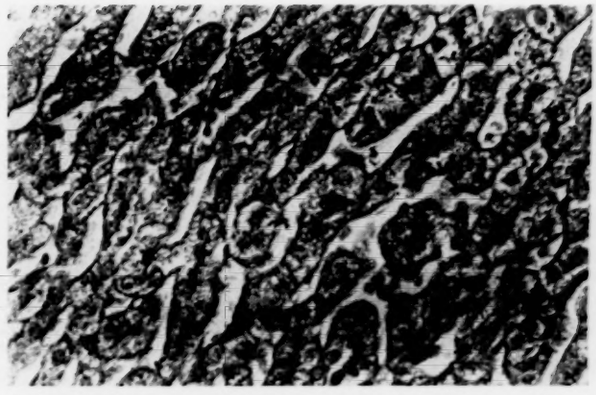


FIG. 7. Family E. Liver biopsy specimen from a thirty-seven year old man. There are fine hemosiderin granules in parenchymal cells. The liver histology is otherwise normal. Perl's stain. Original magnification × 600.

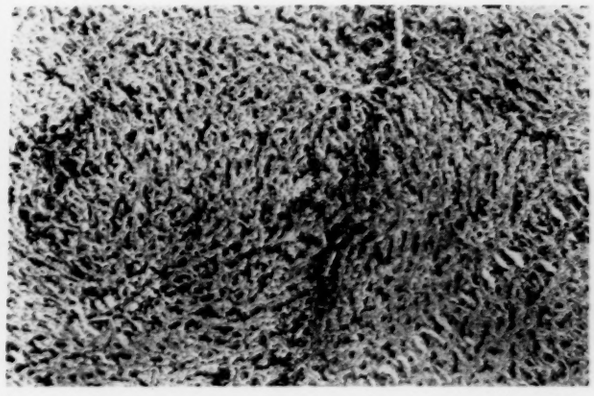


FIG. 8. Family E. Liver biopsy specimen from a thirty-five year old man. Fine and coarse hemosiderin granules are present, chiefly in parenchymal cells but also in Kupffer cells and in the portal tracts. There is a slight increase in portal fibrosis. Perl's stain. Original magnification × 150.

some increased pigmentation, a two-finger hepatomegaly and a raised serum iron level. A liver biopsy specimen showed heavy deposits of iron in hepatic cells with some bands of fibrosis in the portal tracts. (Fig. 10.) Further investigations revealed apparently normal endocrine, hepatic and cardiac function.

COMMENTS

It seems probable that the clinical manifestations of idiopathic hemochromatosis are the end result of tissue damage caused by excessive iron deposits within the body. To understand how such a situation arises it is first necessary to consider some quantitative aspects of iron balance in the normal subject. In an adult male there is about 3 to 4 gm. iron, of which 60 to 70 per cent is in hemoglobin and about 25 per cent in stores. The accumulation of this iron from infancy to adulthood implies a net daily gain of between 0.35 and 0.6 mg. over this period [*12*]. Thereafter the balance in the male remains more or less constant. Only about 0.6 mg. iron is excreted per day and this loss is balanced by the absorption of a similar quantity from the gut [*12*]. In the absence of blood loss the body has little capacity to alter the excretion rate of iron so that when absorption from the gut is increased most of the excess iron is retained within the body. Thus a positive balance of as little as 3 to 4 mg. per day over a period of fifty years will lead to an accumulation of about 50 gm. of iron within the body. From this it is apparent that relatively minor alterations in the absorptive rate of the male can eventually lead to the mas-

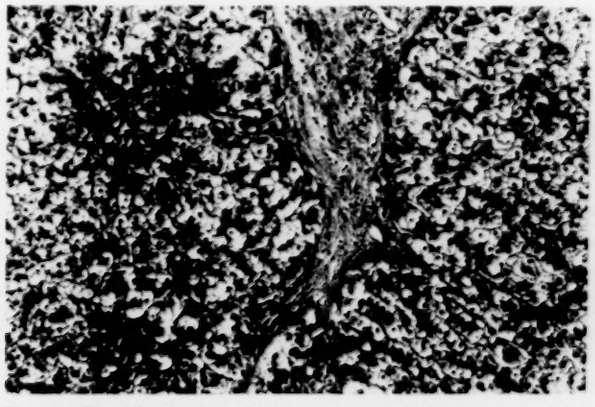


FIG. 9. Family F. Liver biopsy specimen from a twenty-four year old man. Heavy deposits of hemosiderin are present in parenchymal cells and small amounts are also present in Kupffer cells and portal tracts. There is a moderate degree of portal fibrosis. Perl's stain. Original magnification × 150.

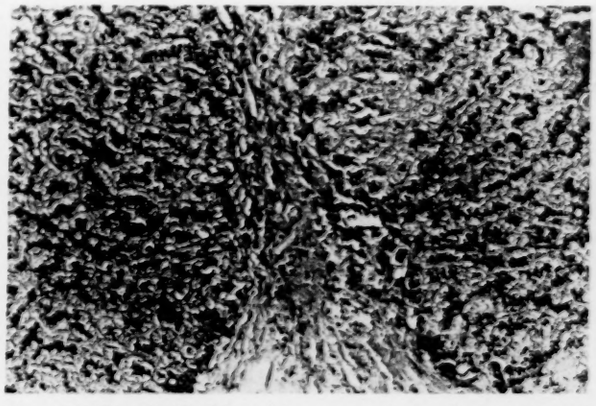


FIG. 10. Family F. Liver biopsy specimen from a twenty year old man. Fine and coarse hemosiderin granules are present in parenchymal cells and to a lesser extent in the portal tracts and Kupffer cells. The portal tracts show a moderate increase in fibrosis with infiltration by lymphocytes, histiocytes and polymorphonuclear leukocytes. Perl's stain. Original magnification × 190.

sive accumulation of iron (30 to 60 gm.) found in idiopathic hemochromatosis at the time when clinical symptoms occur. In the female, however, it is more difficult to establish a positive iron balance since there are the normal losses incurred by menstruation, pregnancies and lactation. Such losses, which probably total between 10 and 15 gm. iron over the average productive life, offer at least a partial explanation for the much lower incidence and the delayed onset of the full blown disease in females [*1*].

Although the clinical features of idiopathic hemochromatosis are relatively characteristic, these only occur at a time when excessive iron has already led to extensive tissue damage, and diagnosis is more difficult in that long latent period when iron is steadily accumulating in the body. Some affected individuals can, however, be detected in the preclinical phase of the disease by other means. It is known that iron overload is usually associated with a rise in the serum iron level and this has proved a useful screening procedure [*1,4*]. In the present study serum iron estimations were carried out on the immediate relatives of patients with idiopathic hemochromatosis and liver biopsy specimens were obtained in most of those with raised levels.

Relatives were chosen as test subjects because there is some evidence that, although most cases of idiopathic hemochromatosis are found sporadically, the disease may be a familial disorder [*1*]. The true incidence is difficult to assess since little attention has been paid to this aspect of the disease. Finch and Finch, who recently reviewed 787 histologically proved cases of hemochromatosis reported in the last twenty years, were able to find only eleven instances in which two or more members of the same family were definitely shown to be suffering from the disease [*1*]. It is, however, doubtful, whether these figures are a true reflection of the familial incidence since there are also a number of instances in which suggestive clinical findings or raised serum iron levels have been described in relatives [*1*]. All except one of these reports [*13*] have recently been extensively reviewed by Boulin and Bamberger [*14*] and by Pirart and Gatez [*15*]. Unfortunately an analysis of the various findings is fraught with difficulty as the criteria for diagnosis have not always been adequate. For example, although the families of thirty-two patients with this disorder appear to have been examined in some detail, only about half of the original cases were proved histologically. In spite of these shortcomings the evidence which is available fits in well with the concept of idiopathic hemochromatosis as a familial disorder.

In the studies on thirty-two families which have been reported in the literature, twenty-six parents were examined. Of these, one was stated to have proved hemochromatosis, five showed clinical evidence of the fully developed disease, two were regarded as subclinical, three were diabetic and one had hepatomegaly. In no instance did more than one parent show suggestive findings.

The results of examination of 107 siblings were even more impressive. There were nine cases proved histologically, twenty-five in whom a firm clinical diagnosis was made, and an additional six who were thought to be probable examples of the disease. In addition, ten subjects had raised serum iron levels, six were diabetic, seven had hepatomegaly and one was suffering from carcinoma of the liver. There was thus some evidence that about half the siblings were affected in varying degrees.

In the present investigation fifty-two immediate relatives of six patients were examined. The most striking findings were in siblings. Of nineteen investigated, three were found to be suffering from the clinical disease and another five showed varying degrees of iron excess on liver biopsy. The incidence of affected siblings may be even higher than these figures suggest since six of the subjects were under the age of twenty years and thus may yet exhibit manifestations at a later date. The significance of the findings in parents and children was more difficult to assess since there was no example of the fully developed disease in a parent and child. There was, however, some evidence to support a hereditary factor. In family B the mother showed a persistently raised serum iron level but the liver biopsy was normal. She gave a history of menorrhagia for many years and it seemed probable that the expression of her metabolic abnormality had been modified by continued blood loss. In family C the father had hepatomegaly and a raised serum iron level but could not be investigated further. It was possible to examine the children of affected persons in only two families. In family A there were three children. One of the daughters, aged twenty-two years, had a high serum iron level and hepatomegaly but refused further investigation. In family F most of the children were very young and appeared normal. However, two adolescent children of an affected female had raised serum

iron levels. In both the liver biopsy findings were normal.

Although these results are not sufficiently complete to permit firm conclusions, they do allow for some speculation as to a possible genetic linkage in idiopathic hemochromatosis. In two of the five families in which parents were examined there was some evidence that one parent in each family was affected. In a third family the mother was diabetic but otherwise normal. In a fourth family the mother, who suffered from menorrhagia and had given birth to fourteen full term infants, appeared healthy but her brother had died previously from diabetes. The significance of these latter findings is difficult to evaluate. (It should, however, be noted that although the diabetes which occurs in idiopathic hemochromatosis is almost certainly due to iron deposits in the pancreas, a higher incidence of diabetes in otherwise unaffected relatives has been noted previously [*14*]. In addition, it has been possible to increase iron absorption experimentally by ligating the pancreatic ducts [*16*] and by damaging the pancreas [*17*]). In the last family the mother was normal but the father had succumbed previously to heart failure at a young age and may possibly have suffered from the disease. All this evidence is at least compatible with the idea that a parent in each of the families examined was suspect in one way or another.

In siblings the findings were much more concrete, since about 50 per cent of those over the age of twenty years showed histologic evidence of varying degrees of iron overload. Finally, there was suggestive evidence that three children of two affected parents were suffering from the metabolic defect. These data therefore fit in well with the concept that idiopathic hemochromatosis is a familial disorder, and they lend some support to Neel and Schull's thesis that it is due to an autosomal gene of incomplete penetrance which is transmitted as a Mendelian dominant [*18*]. Whether, in fact, the penetrance is incomplete is difficult to evaluate from the available data. The present findings would also be compatible with a more complete degree of penetrance but a variable expressivity. The resolution of this problem will be possible only when the nature of the fundamental biochemical defect is discovered. Meanwhile it would be helpful to have data on the rate of absorption of iron from food in seemingly unaffected parents, and to know whether or not the apparently higher incidence of diabetes in relatives, unaccompanied by iron excess, has any significance.

The possibility that common environmental factors, such as unusual eating habits, might explain the present findings seems hardly tenable since affected siblings had been living in different localities for long periods prior to the study. Nevertheless it is probable that the clinical expression of the disease in subjects with a similar degree of absorptive defect can be modified by other factors, such as the amount of iron in the diet and the amount of iron loss from the body, e.g., menstruation and pregnancy. In addition, many workers have noted the higher incidence of alcoholism (± 30 per cent) in patients with the clinical disease [*1*]. Whether such an abnormal diet increases iron absorption or potentiates damage to the liver and thus accelerates the onset of the symptomatic stage of the disease is not known. However, the fact that no example of the fully developed disease in different generations was found in the present series cannot be explained on environmental factors alone and seems rather to represent a variability in expressivity of the abnormal gene. On the other hand the severity of the metabolic defect in affected members of the same generation is remarkably constant. Thus in two of the present families there were five affected siblings, all of whom showed severe involvement in the third decade of life. In a third family four brothers appeared to have an absorptive defect of about the same intensity. In this family two sisters were also probably affected to a similar degree but the iron stores were not as large. This difference could well be explained by the ameloriating effects of blood loss via menstruation.

A surprising finding was the poor correlation between the raised serum iron levels and the degree of iron overload as judged by liver biopsy findings. In subjects with a high serum iron the hepatic histology ranged from normal to the changes of fully developed idiopathic hemochromatosis. In subjects with normal biopsy findings it was thought that there might be still some increase in non-stainable iron in the liver but the response to venesection showed little if any difference from normal. Although the biologic significance of a high serum iron level in subjects with normal iron stores is not clear, it could be a reflection of an abnormal gradient between the iron in cells and plasma. Whatever the explanation it is obvious that a raised serum iron level is not of itself a good indication of the degree of iron overload. In most instances the total iron-binding capacity was also measured.

Although the mean value in affected relatives was somewhat reduced (285 μg./100 ml.), the results were not definite enough to be useful diagnostically.

For a better understanding of the amount of excess iron in relatives with high serum iron levels, liver biopsy was extremely helpful. Using the technic it was possible to demonstrate the various phases in development. In the early stages the iron was found as discrete granules of hemosiderin in hepatic cells, either finely dispersed throughout the liver lobules or in focal scattered areas. With greater quantities, the iron aggregated together into coarser masses and was uniformly distributed throughout the lobules. With marked iron excess there was a slight to moderate increase in fibrosis of the portal tract but a true monolobular cirrhosis was seen only in association with the fully developed clinical disease.

Although idiopathic hemochromatosis is a relatively rare disorder it is probable that familial studies of the present type would uncover a considerable number of affected indivduals, especially in siblings of patients suffering from the disease. The detection of affected subjects in the preclinical phase of idiopathic hemochromatosis is of some practical importance since the excess iron can be removed by repeated venesections [*2,3*]. The rigorous use of such therapy should prevent or arrest the development of tissue damage in such individuals [*19,20*].

SUMMARY

Fifty-two immediate relatives of six patients suffering from idiopathic hemochromatosis were examined. In eleven subjects with raised serum iron levels three were found to have the fully developed disease while five others showed varying degrees of iron excess on liver biopsy.

The present results support the concept that idiopathic hemochromatosis is a familial disorder in which the absorption of excessive amounts of iron from the gut eventually leads to massive accumulation of iron within the body. The disorder is probably the result of an autosomal genetic defect of incomplete penetrance and/or variable expressivity which is transmitted as a Mendelian dominant.

The practical value of familial studies in idiopathic hemochromatosis is stressed since affected persons can in this way be detected and treated in the preclinical phase of the disease.

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The Pathology of Psittacosis*

A Report of Two Cases with Hepatitis

ELLARD M. YOW, M.D., J. CHARLES BRENNAN, M.B., B.CH., JANE PRESTON, M.D. *and* SAMUEL LEVY, M.D.

Houston, Texas

PSITTACOSIS or ornithosis is one of the few infectious diseases increasing in frequency of occurrence. The number of reported cases in 1956 was 508, as compared to 278 in 1955, an increase of 90 per cent [*1*]. This increased incidence has been due largely to the marked increase in the number of psittacine birds being imported and raised, and utilized as household pets. In Texas the transmission of the infection from domestic fowl has become a problem of some proportion. Between 1948 and 1952 there were five outbreaks among poultry workers, with clinical illnesses in 196 persons and seven deaths [*2*]. From 1952 to 1954 there were 264 additional cases, occurring primarily in persons picking and dressing turkeys [*2*]. The disease in human beings has been contracted from other non-psittacine birds, including pigeons, chickens, ducks, pheasants, and even the lowly "road runner" [*2*].

Psittacosis varies widely in its clinical manifestations. The incubation period usually is stated as varying from seven to fifteen days, but an incubation period of from thirty to thirty-nine days has been suspected. In the 1951 Giddings fowl-borne outbreak the incubation period in 17 per cent of cases was from five to sixteen days, the mean being eight days. The shorter incubation periods occurred in workers in the picking room, presumably because of heavier exposure to infected particles [*2*].

The virus of psittacosis is present in the blood, tissues and discharge of infected birds. It is usually transmitted by the inhalation of dried excreta of the bird but may also be contracted by handling infected tissue and, rarely, through bites. While most diseases transmitted from animal to man are not easily transmissible from man to man, well documented cases of man to man transmission of psittacosis have been reported. The classic example is the 1943 Louisiana epidemic in which eighteen persons contracted the disease directly or indirectly from one patient [*3*]. There were eight deaths in the epidemic and all fatal infections transmitted from human to human occurred among those exposed to sick persons within forty-eight hours prior to death. There was no spread from non-fatal cases. There are other isolated examples of the disease being contracted from other human beings but in most epidemics this has been rare [*4,5*]. There have been no proved cases of transmission by this route in the Texas epidemics [*6*].

Psittacosis is apparently quite rare in children under ten years of age. Only six such cases have been reported, four in England, one in California and one in Germany [*7*].

The disease may be transmitted by healthy birds acting as carriers of the psittacosis virus, but generally the attack rate and the severity of the illness is related to the inoculating dose [*8*]. Thus birds having active infections are more likely to transmit the disease than asymptomatic carriers.

The severity of psittacosis varies a great deal from a very mild and transient influenza-like illness to an abruptly beginning illness with high fever, severe headache, non-productive cough, progressing in some cases to delirium and death. In an occasional case the onset is gradual and insidious. It is generally believed that most patients with the disease are quite sick, with chilly sensations, fever, severe headache, myalgia, nausea and vomiting. There is reason to doubt that the severe form represents the typical case, but nevertheless it does represent the problem case. The usual course of the severe infection is that of acute onset of fever, between 103° to

* From the Ben Taub Infectious Disease Research Laboratory, Jefferson Davis Hospital and the Departments of Internal Medicine and Pathology, Baylor University College of Medicine, Houston, Texas.

105°F., remaining high for seven to ten days, then declining by lysis during the second or third week. Characteristically there is a relative bradycardia.

In birds, the primary sites of the disease are the liver, spleen and pericardium. In human beings, the lung is the organ most consistently involved although occasional patients exhibit no clinical or roentgenographic evidence of pneumonia. As is true of the other viral forms of pneumonia, the usual physical findings are not obvious during the first few days of fever. Even changes of the pneumonia as seen in the x-ray films may not appear until later in the course of the illness. The sputum is quite scanty and increases in severe illnesses and during the stage of resolution. It is non-purulent and mucoid in character. Of particular clinical interest is the relatively inconspicuous cough, in contrast to the severe cough so characteristic of most other forms of viral pneumonia. While some patients complain of pain or soreness in the chest, true pleuritis is quite rare. This is surprising in view of the polyserositis of the disease in birds. Splenomegaly is sometimes noted for a few days toward the end of the first week of illness. This is more common in those patients with serious illnesses. Signs and symptoms of pulmonary insufficiency are seen only in the most severe cases.

The leukocyte count in psittacosis is usually low, but occasionally is slightly above the normal range. The most helpful laboratory aid in the diagnosis of the disease is the rising titer of complement-fixing antibodies. These antibodies are usually demonstrable during the second week of the disease but in some cases there may be a delay of three or four weeks. This is especially likely to occur if patients have had suppressive antibiotic treatment early in the illness.

It is quite difficult to estimate accurately the mortality rate in psittacosis. It has been reported to be from 10 to 40 per cent. This figure is undoubtedly exaggerated by the recognition of the disease primarily in epidemics and in the seriously ill sporadic patient. There is evidence, however, of increased severity of the disease in persons above the age of forty.

Both experimental and clinical evidence indicates that the tetracycline group of antibiotics exert a suppressive effect upon the psittacosis virus. Since these drugs are not usually virucidal in this disease therapy must be begun early and continued for two to three weeks to have optimal effect.

It is surprising that in view of the reported mortality of psittacosis there is such a paucity of information regarding the pathology of this disease in human beings. The most profound lesions in man as in other mammals are characteristically those produced in the lungs. In less typical cases, but usually in those patients presenting more severe clinical signs, the liver, spleen and rarely the brain (leptomeninges) show the specific lesions in profusion. In these patients the pathology at autopsy may closely resemble the disease as seen in birds.

The pulmonary lesion is a lobular interstitial pneumonitis. This lesion commences at the hilum, extends to the periphery, and appears eventually to be dominant in the dependent lobes and segments. It is not usually accompanied by secondary bacterial invasion [*9*]. At first there is a tremendous outpouring of fluid from capillary vessels, filling alveoli and distending interstitiae. Occasionally this exudate, which is usually very rich in fibrin, is accompanied by small hemorrhages from damaged capillaries. Polymorphonuclear leukocytes occur in the fluid exudate early, but disappear and are not usually found in the exudate in later stages of the disease. Dominant in the exudate usually encountered in the autopsied cases are large numbers of mononuclear histiocytes in the alveoli and interstitial spaces; there is an accompanying proliferation and considerable desquamation of alveolar lining cells. Few to moderate numbers of lymphocytes and some plasma cells are seen in the exudate later. A close search will not infrequently result in the finding of intracytoplasmic elementary granules or inclusions of coccobacillary form in the large mononuclear cells. Frequently parasitized cells will have a ballooned cytoplasm and nucleus. The inclusions are not specific for psittacosis as demonstrated by electron microscopy [*10*].

The trachea and major and minor bronchi participate in the inflammatory process, and Forbus [*11*] was impressed by the interstitial mononuclear reaction in the bronchus as in the alveolar walls. The dilated peribronchial lymphatics, swollen mucus-secreting glands, interstitial tissues heavily infiltrated with mononuclear cells, and proliferative and degenerative changes in bronchial epithelium with associated minute ulcerations of the mucosa reflect the severity of the reaction here. The accompanying thick, blood-stained, gelatinous, viscid plugs of mucus that fill the major and minor bronchi

are very striking when one considers the clinical features of anoxia. Even at autopsy these mucous plugs are difficult to dislodge. Some workers have not been so impressed with these bronchial changes [*12,14*] while others have commented on their severity and occurrence in "chronic" cases [*15*]. Frequently one finds foci of necrosis in the more affected areas of the lungs. These will not infrequently be associated with minute platelet-like thrombi of alveolar capillaries. Such areas may have increased numbers of polymorphs and red blood cells within and about them.

The affected areas of the lungs become consolidated, but with a rubbery gelatinous consistency that is almost pathognomonic of the nature of the process. There is much less resistance to the cutting knife edge than in lobar pneumonia, and characteristically the affected areas of the lung are remarkably free of oozing of fluid, while blood in the vessels of the lung presents an odd "inspissated" appearance. The sharply outlined zones of demarcation of involved and uninvolved lobules of lung recorded by Binford and Hauser [*12*] are not generally described in reports but have been noted by us, as has the occasional groupings of air or serum-filled alveoli in otherwise consolidated areas.

The pulmonary inflammation is imitated in the hilar lymph nodes where large numbers of swollen mononuclear macrophages distend the afferent lymphatic sinuses. Mild to moderate proliferative changes are found in the germinal centers. The lymph nodes are usually very swollen, edematous and rubbery.

These pulmonary and hilar lymph node changes do not appear to differ significantly on histological grounds alone from the pneumonitis of influenzal pneumonia or from published descriptions of other viral or rickettsial pneumonias; indeed they have been described following experimental introduction into the lung of a variety of toxic substances [*11*].

In the spleen the gross and microscopic features are those of acute splenic tumor; a mild reticuloendothelial proliferation may occur, and in some cases focal necroses have been described. Parasitism of splenic histiocytes has also been described.

Changes in the liver [*11,19*] characteristic of the condition are those of a "non-specific reactive hepatitis" in nature, and are confined usually to intralobular focal necroses of liver cells; the degenerate cells are surrounded by hyperchromatic swollen Kupffer cells, occasional lymphocytes, and rare polymorphonuclear leukocytes; Kupffer cell hyperplasia is noted frequently throughout the liver, often with erythrophagocytosis and cytophagocytosis, and not infrequently cellular parasitism of the Kupffer cells by the psittacosis elementary bodies has been reported. A variable mononuclear cell increase in the portal tracts and a mild degree of fat accumulation in liver cells have been described also.

The cardiovascular system also may be involved in psittacosis. At autopsy, changes described include dilatation of the right side of the heart, hypertrophy of cardiac muscle, cloudy swelling and fatty degeneration of the myocardium, interstitial edema, interstitial infiltration with plasma cells and lymphocytes, and subendocardial hemorrhages especially in the region of the mitral, aortic and bicuspid valves. Interstitial myocarditis has been observed in a fatal case in a child. There may be signs of general vascular damage as manifested by hemorrhage from the nose and cutaneous petechiae [*13*].

Occasional to many hyaline glomerular capillary occlusions have been described in the kidneys [*12*]. Most patients have been reported to have had albuminuria.

Various reports [*16–18*] have described a macrophagic and fibrinous or gelatinous arachnoiditis about the Sylvian fissures in the brain and medial portions of the cerebral hemispheres, but usually no demyelinization nor neuronal degenerative changes have been noted. Walton [*17*] reported intracytoplasmic elementary bodies in macrophages in meningeal exudate in one patient presenting severe signs in the central nervous system.

In September 1946 two outbreaks of psittacosis occurred among employees of two poultry packing plants in Houston. There were twenty employees in each plant involved in processing and shipment of turkeys from a single farm in Waller, Texas. A detailed epidemiologic study is being reported elsewhere [*20*], but among the forty workers there were twenty-four patients with clinical and laboratory evidence of psittacosis and an additional group of three patients with increasing titers of complement-fixing antibodies without clinical evidence of infection.

Of the twenty-four patients with clinical illnesses, twenty were followed as out-patients and four were hospitalized. All but two of the patients

had relatively mild illness which either subsided spontaneously or responded promptly to tetracycline therapy. The most common complaints were headache, fever, myalgia, cough and anorexia. The major complaint in most cases was headache, which was usually generalized, dull, and not related to position or directly to temperature.

While fever was found in only nineteen of the patients, it is probable that the temperature elevation was missed in some of the out-patients. The temperature went as high as 105°F. in the patients most severely ill, but most patients had a temperature in the range of 100 to 101°F. Cough was a complaint in seventeen of the twenty-four patients, but it was quite mild and non-productive in all but one of the patients. In this patient the sputum was mucoid and tenacious, but contained no blood grossly. Myalgia, present in seventeen patients, was usually generalized, but was predominantly in the back and shoulders in three. These same three patients complained of pain on flexion of the neck. Pain in the chest was moderately severe in two patients. It was aggravated by deep breathing but was not typically pleuritic in character. Dizziness was a fairly common complaint; it was ill defined, being described as "light-headedness" and not characteristic of true vertigo. Dysuria was a complaint in two hospitalized patients and was associated with suprapubic discomfort.

The urinalyses in these patients were normal. Diarrhea and constipation were rare complaints and were mild and self-limited.

There was a paucity of physical findings in all but two of the most seriously ill patients. Splenomegaly was observed in only one of the non-hospitalized patients, occurring six days after the onset of fever. Two of the hospitalized patients exhibited evidence of pharyngitis, and one of them had severe lymphadenopathy, hepatomegaly, and a brief episode of disorientation.

Two of the patients studied in this epidemic were severely ill, and one died. Both of these patients presented clinical and laboratory evidence of hepatitis and altered renal function. Pathologic studies have often revealed microscopic areas of focal necrosis in the liver of patients dying of psittacosis, but clinical jaundice has not been previously reported. For this reason these two patients are presented in more detail, together with a discussion of the pathologic changes observed in the patient dying of the disease.

CASE REPORTS

CASE 1. A sixty-three year old Negro poultry processor was admitted to Jefferson Davis Hospital on September 10, 1956, thirteen days after exposure to a flock of turkeys subsequently proved to have psittacosis. His job at the poultry plant consisted of general janitorial work in addition to securing live fowl to an assembly line and decapitating them. One week after exposure he had sudden onset of fever, headache, myalgia, anorexia and a cough productive of small amounts of tenacious sputum. He was seen by a physician but refused to take the prescribed medication. His symptoms progressed, and three days later he saw his regular physician who prescribed chlortetracycline therapy. The patient took 250 mg. every four hours for forty-eight hours by the oral route. At the end of this time he was somewhat improved and the medication was voluntarily discontinued. The following day the patient had an episode of mental confusion, urinary incontinence, and an increase in severity of all previous symptoms. By the next day he had become continuously disoriented and his wife noticed that his eyes were yellow. He was brought to the hospital for admission approximately one week after onset of his illness.

On admission to the hospital the patient was found to be disoriented and critically ill. His temperature was 102°F., pulse 100 per minute, respiratory rate 5 per minute, and blood pressure was 108/72 mm. Hg. His sclerae were very icteric. The examination of the optic fundi revealed early arteriolar degenerative changes. The skin and mucous membranes were dry. There was no significant lymph node enlargement. The nose and throat were normal and the neck was not stiff. Examination of the chest revealed a rapid respiratory rate with dullness of both lung bases. Coarse rhonchi and inspiratory and expiratory sibilant rales could be heard over both lung fields. The heart was slightly enlarged by percussion, but no murmurs or arrhythmias were noted. The abdomen was slightly distended and the liver and spleen were both palpable. There were no significant neurologic changes other than the alteration in sensorium. Rectal examination revealed a slightly enlarged prostate.

On admission, laboratory examination revealed a hemoglobin of 12.4 gm. per cent with a hematocrit of 37 volumes per cent. There were 10,100 white blood cells/cu. mm., with 89 per cent segmented polymorphonuclear leukocytes and 2 per cent nonsegmented neutrophils and 9 per cent monocytes. A serologic test for syphilis was negative. The psittacosis complement-fixation reaction was positive in a dilution of 1:16. The urine specific gravity was 1.025 with 20 mg. per cent of protein. An occasional white cell was seen on microscopic examination. The test for sugar was negative. The serum bilirubin was 7.2 mg. per cent; thymol turbidity 3; and alkaline phosphatase 2.6 Bodansky units. Prothrombin activity was 71 per cent. The serum total protein was 7.0 gm.

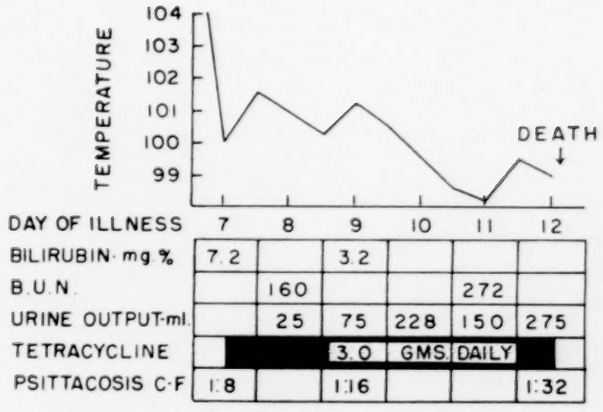


FIG. 1. Case 1. The clinical course of a sixty-three year old poultry house worker dying of psittacosis.

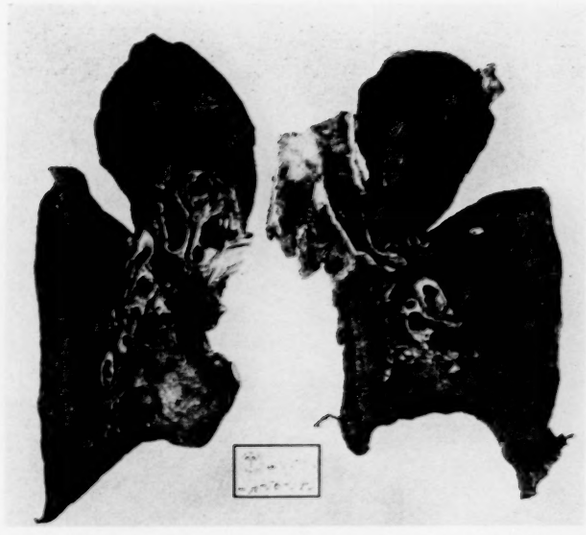


FIG. 2. Case 1. The gross appearance of the lungs in the patient dying of psittacosis, illustrating consolidation of both lower lobes. The trachea and major bronchioles contained mucoid plugs and numerous erosions of the mucosa.

per cent with albumin 4.3 and globulin 2.7. The blood urea nitrogen was 160 mg. per cent, creatinine was 12 mg. per cent, CO_2 8.5 mEq./L., sodium 139 mEq./L., and potassium 4.3 mEq./L. Skin tests for tuberculosis, blastomycosis, histoplasmosis and coccidioidomycosis were negative. Serum agglutinations for leptospiral diseases were negative and no leptospirae were seen in dark field examinations of the urine. A muscle biopsy was normal. Cold agglutination tests were negative as was the direct and indirect Coombs' test. The platelet count was 250,000/cu. mm., bleeding time was twenty-eight seconds, and clotting time (Lee-White) was four minutes.

The initial portable chest roentgenogram was of poor quality but revealed pneumonic infiltration of the right lower and middle lobes.

With hydration and intensive tetracycline therapy, the patient's temperature returned to normal by the second day in the hospital. His respiratory effort seemed to decrease but the urinary output was less than 100 cu. cm./day. On the third day there was an episode of hematemesis. By the next day the blood urea nitrogen had risen to 272 mg. per cent and the patient was totally anuric. The jaundice was decreasing; the bilirubin fell from 7.2 mg. per cent to 3.2 mg. per cent and the electrolyte disturbances were corrected. There was evidence of progressive respiratory insufficiency and general weakness. The patient died on the sixth day after admission to the hospital. (Fig. 1.)

The autopsy examination was begun seventeen hours after death, the body having already been embalmed. External examination revealed a well developed, well nourished Negro man, with slightly injected conjunctivae and icteric sclerae.

The right lung weighed 800 gm. and the left lung 650 gm. The lungs presented similar appearances bilaterally. (Fig. 2.) The right middle lobe, right lower lobe, and left lingular segment and left lower lobe in their entirety were consolidated and cut with very firm consistency. The surfaces of these consolidated lobes presented prominent blood vessels, bronchi, and interstitial tissue septums, all stained greenish yellow as by bile. The bronchi were full of a very tenacious jelly-like dark gray mucoid material. The blood vessels were distended with an inspissated viscid blood. The pleural surfaces of the lungs were mottled, pale blue-pink, and slate gray, and fine fibrinous adhesions covered the superior lobes on each side. The upper lobes on each side were slightly crepitant but very congested, slightly edematous, and presented focal areas of increased consistency or irregular distribution. Very little fluid exuded from the cut surfaces of the lungs, and that mainly from the upper lobes. The cut surfaces of the lower lobes were dry and firm. Removal of the mucoid plugs from the bronchi revealed ecchymoses and many erosions of the major bronchial and lower tracheal mucosa. There were similar ecchymoses throughout the laryngeal mucosa. There was no evidence of embolism or infarction, and no thrombi were formed within pulmonary vessels. Hilar lymph nodes were all enlarged, soft, and dark with carbon pigment. Some were twice the usual size and edematous.

The liver appeared slightly enlarged, weighing 1,700 gm. The lobar configuration was normal. The margins were slightly rounded. There was a slight accentuation of lobular markings evident through the capsule. On the cut surface individual lobules appeared swollen, and occasionally very tiny gray-white specks were visible in some lobules. There was a slight increase in bile staining of the entire liver. The intrahepatic vascular and biliary tracts were normal. The extrahepatic biliary duct system was patent. The spleen weighed 100 gm. and was firm on the cut surface. The capsule was very slightly thickened, and

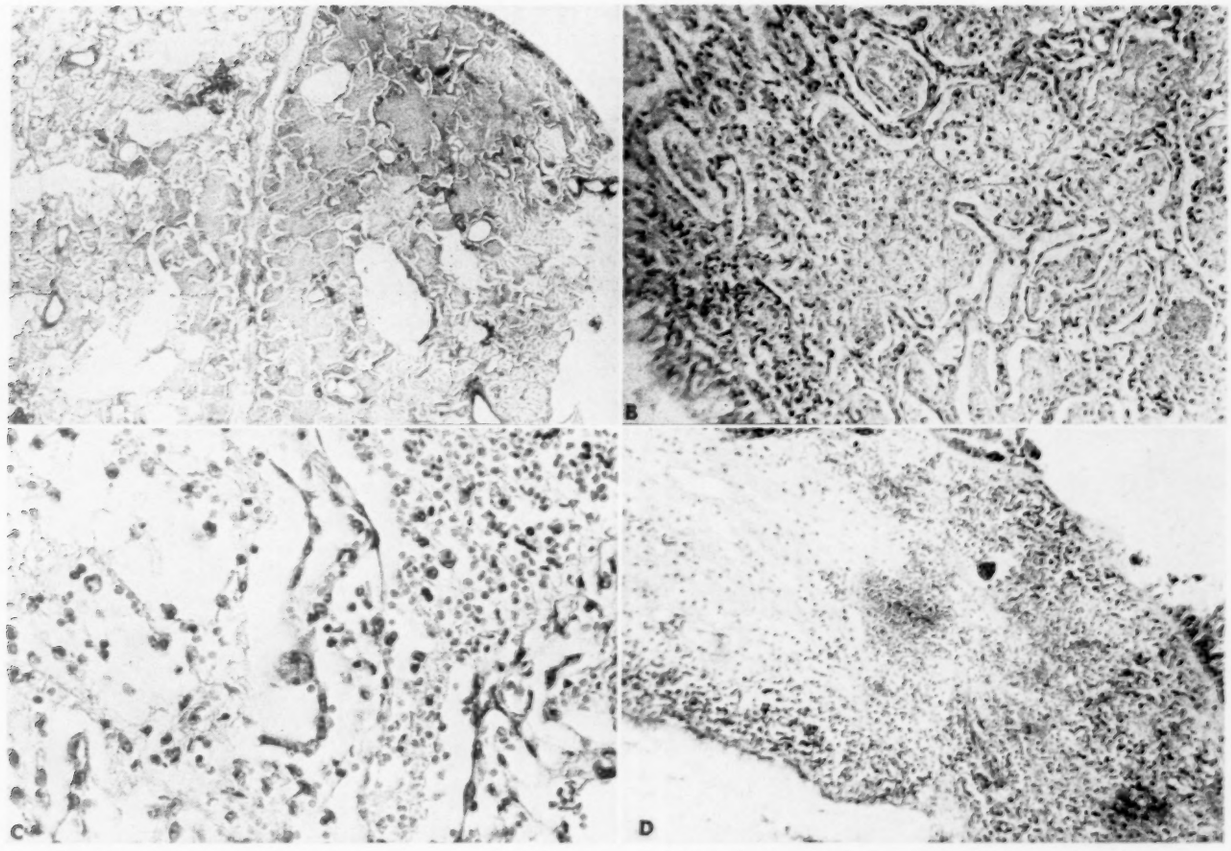


FIG. 3. Case 1. A, the alveoli of the lung were filled with a pinkish gelatinous exudate. B, the interstitial spaces were swollen and contained many mononuclear cells. C, a high power view of the lung illustrating the large mononuclear cells and red blood cells, but relatively few polymorphonuclear leukocytes. D, erosion of the mucosa of a major bronchus with submucosal inflammation.

there was apparent slight to moderate increase in connective tissue elements on the cut surface. The pancreas weighed 180 gm. and appeared grossly normal. Many large and small ecchymoses were seen in the mucosa of the intestinal tract from the esophagus to the rectum.

The right kidney weighed 200 gm., the left 220 gm., and apart from slight variation in size and lobular configuration their gross appearances were similar. The capsules were tense, and slightly difficult to strip, but quite thin. The cortices were slightly thickened in width and diffuse gray-white; the intricate glomerular and tubular pattern was less distinct than normal. The cortex bulged slightly on cutting. The medullary pyramids were not significantly altered. Ecchymoses were present in the renal pelvic mucosa, also in the ureter mucosa. The urinary bladder mucosa was irregularly hemorrhagic, the muscular wall slightly hypertrophied, and ureteral and urethral orifices were patent. The prostate was slightly hypertrophied in its lateral areas. The testes, parathyroid, thyroid and adrenal glands were relatively normal. There was a pigmented adenoma of the right adrenal cortex, 1 cm. in diameter.

The brain weighed 1,195 gm. and appeared dry and relatively bloodless. There was minimal atherosclerosis of the vessels at the base of the brain. The leptomeninges were transparent.

Extra microscopic sections were stained as needed by Verhoeff s, Nobel's modification of Machiavello's, and by Giemsa methods. Several sections were taken from all lobes of the lungs. The histological lesions revealed a diffuse interstitial pneumonitis of all lobes, but especially of the lower lobes, and chronic passive congestion in the lungs, with areas of fibrous pleural adhesions over the apical areas. The interstitial pneumonitis was characterized by a widespread intra-aveolar and interstitial exudation of pinkish fluid very rich in fibrin; the staining changes in this exudate suggesting that it was partly mucinous in character, inspissated, and relatively free of water. (Figs. 3A and 3B.) Especially in the lower lobes, there was swelling of large mononuclear cells lining the alveoli. The alveoli also contained exudates of fibrin and red blood cells and, more frequently, of large tissue histiocytes, with occasional lymphocytes and very occasional polymorphonuclear leukocytes; mononuclear cells were frequently seen in the interstitial

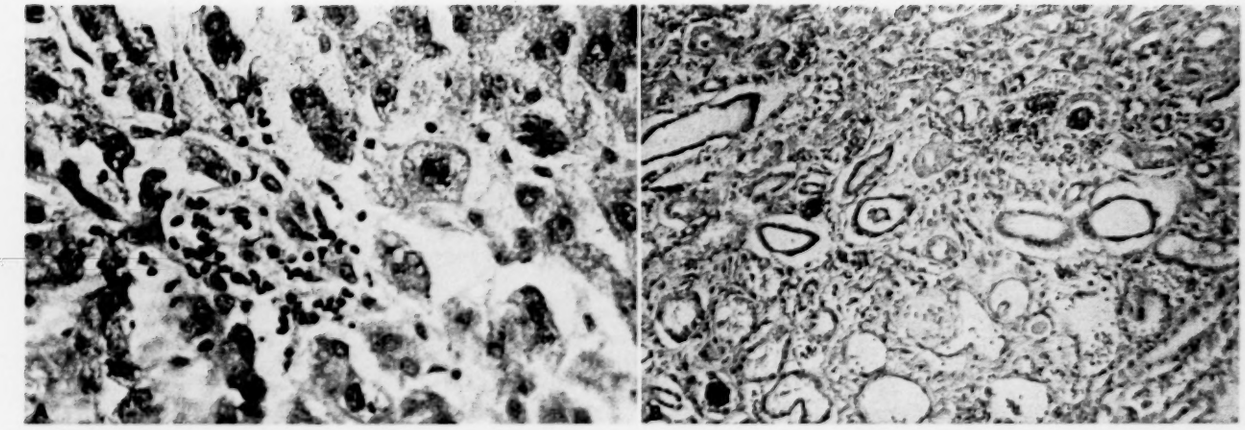


FIG. 4. Case 1. A, microscopic section of the liver, illustrating hyperplasia of the Kupffer cells and hepatic cell injury. B, microscopic section of the kidney. The distal and convoluted tubules contained protein material and occasionally leucine casts.

tissues especially about major and minor bronchi. (Fig. 3C.) The alveolar exudate varied in composition, but mostly consisted of mononuclear cells, small and large, in various stages of phagocytosis, some large macrophages with ingested red blood cells or polymorphs, or fragmented nuclear material, some lymphocytes and a few red blood cells in a fibrinous matrix. The large mononuclear cells varied from 12 to 20 microns in diameter. Occasionally many desquamated alveolar lining cells were present, and often mitotic activity was noted in these. Frequently the nuclei of these cells were ballooned; often the cytoplasm of both these cells and the mononuclear cells were ballooned irregularly and contained very small pleomorphic basophilic bodies. There were areas in which this exudate in the alveoli presented evidence of early organization. There were frequent small and large areas of ulceration of the lining epithelium of the bronchi and bronchioles. (Fig. 3D.) Foci of parenchymal necrosis were evident in some areas. Intraalveolar cellular exudate was greatest in the lower lobes. Occasional arterial, venous and capillary thrombi were present.

Sections of the bronchi revealed foci of considerable hyperplasia of bronchial epithelium, and also erosions of the lining respiratory epithelium over areas of intense congestion of the tunica propria, while tissue histiocytes with some lymphocytes, occasional plasma cells and eosinophils infiltrated the interstitial tissue between the mucous secreting glands in the bronchial wall. The mucous glands were widely dilated with mucus secretions. Sections of the trachea revealed numerous foci of recent hemorrhagic extravasation in the tunica propria, associated with overlying erosions of the tracheal mucosa. There was considerable fibrinous edema of the interstitial tissues of the tunica propria, and in areas of erosion there were infiltrates of lymphocytes, large numbers of eosinophilic mononuclears and occasional polymorphonuclear leukocytes.

There was edema and dilatation of the lymphatic sinuses of the peribronchial lymph nodes, with thick fibrinous fluid containing very numerous large macrophages and some red blood cells and lymphocytes. The macrophages were variable in form, as in the alveolar lung exudate.

Sections taken from different areas of the ventricular myocardium revealed extreme congestion of capillary vessels and some generalized hypertrophy of the muscle fibers. Despite a close search for foci of necrosis, none were found. There were occasional areas of increased interstitial tissue about small vascular channels in the myocardium, and frequently small collections or clusters of large, pink macrophages were present in these areas. The epicardium, pericardium and endocardium were relatively normal.

The liver capsule was normal. All capillary vessels were congested with blood. The portal triads contained infiltrates of lymphocytes in varying numbers. The hepatic artery radicals, the branches of the portal veins, and the bile ducts, appeared relatively normal. The architecture of liver lobules was preserved. In the majority of liver lobules, however, there was atrophy of cells about the central veins with some slight collapse of the reticulum in these areas. There was obvious hyperplasia of Kupffer cells in some areas, relatively little in others. Their cytoplasm contained granular lipochrome pigment. Many of the liver cells in the centrilobular areas had hyperchromatic nuclei of varying size; many contained increased amounts of finely granulated pigment. Occasional fatty cysts of liver cells were present in the centrilobular and mid-zone areas. Occasionally small clusters of macrophages were present about individual necrotic foci of liver cells scattered haphazardly in many lobules. (Fig. 4A.)

Microscopic examination of the kidneys revealed that all glomeruli were congested and many were excessively lobulated, with increase in collagen in glomerular basement membranes. Many Bowman's

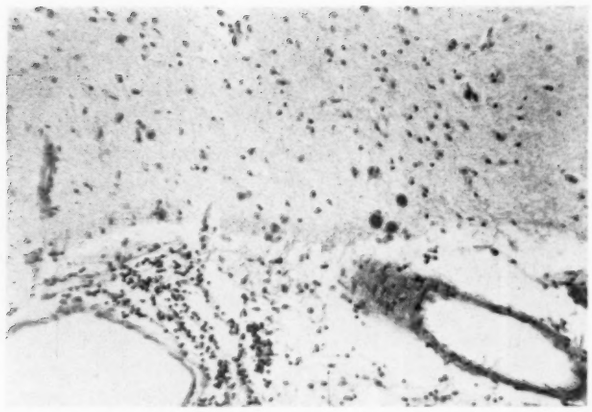


FIG. 5. Case I. Microscopic section of brain and meninges, illustrating increase in numbers of mononuclear cells.

spaces contained protein-like material. The proximal tubules were slightly dilated and filled with proteid material, while the lining cells were frequently swollen and frayed. Some of the tubules contained leucine crystals. Distal tubules and convolutes contained casts of proteid material, and occasionally these contained enmeshed red blood cells and white blood cells, while often casts were stained a yellow-green color and leucine crystals were numerous in them. The distal tubules also were dilated. (Fig. 4B.) Collecting tubules contained casts of partially hemolyzed red blood cells, protein, and some casts of mixed red and white blood cells. The interstitial tissues were edematous, especially in the juxtamedullary areas. There was slight intimal thickening by fibrosis of major arteries, but arterioles were relatively normal. In the renal pelvis there was lymphocytic infiltration about the venules in the tunica propria of the pelvis. Small numbers of these inflammatory cells were present about lymphatics and venules in interlobar areas. Sections of the prostate gland, including a portion of the mucosa of the urinary bladder and prostatic urethra, revealed insignificant inflammatory changes of mild degree, most obvious in the tunica propria of the prostatic urethra.

The capsule of the right adrenal gland was slightly thickened by fibrous tissue and occasionally contained small infiltrations of lymphocytes. There was a diffuse and focal hyperplasia of adrenal cortical cells, and there was one partially encapsulated tumor nodule, 1 cm. in diameter, apparently arising from the medullary aspect of the cortex. This nodule was formed of a loose connective tissue supporting highly pigmented, frequently hyperchromatic cortical cells that were apparently proliferating. The cells in the adenoma adhered in clusters and small columns that tended to imitate the architecture of the zona reticularis of the cortex. There were considerable amounts of mature fat cells in the stroma forming this cortical adenoma. There were many foci of atrophy of the cells of the adenoma, collections of lymphocytes and plasma cells being grouped in the areas of atrophy. There was no evidence of malignancy. The adrenal medullary tissue was minimal in amount, and normal. The pulp and sinusoids were very congested with blood and there were occasional minute foci of interstitial hemorrhage and collections of macrophages in the pulp and sinusoidal tissues in the spleen. There appeared to be some increase in reticular connective tissue at the expense of the lymphoid tissue of Malpighian corpuscles. Reticuloendothelial cells were swollen and hyperchromatic. There were minor degenerative changes in the major arterial vessels.

Sections of the thyroid gland were normal. Sections of leptomeninges revealed a moderate increase in mononuclear cells, mostly lymphocytes and plasma cells with some macrophages, in the edematous connective tissue of leptomeninges about the cerebral cortex, cerebellum, midbrain, medulla oblongata, hypothalmus and hippocampal gyrus. (Fig. 5.) There was mild hyaline change in walls of arterioles throughout the cerebrum. Very occasional small petechiae were present in the gray and white cerebral matter. Evidence of intracytoplasmic elementary bodies was lacking in meningeal exudate. In the hypothalamus there was a small focus of necrosis filled with gitter cells in the genu of the internal capsule, with only slight hyperplasia of surrounding astrocytes. There was mild ferrocalcinosis of the media of adjacent blood vessels in the globus pallidus, but no vascular occlusions.

CASE II. A sixty-five year old Negro poultry processor was admitted to St. Elizabeth's Hospital on September 13, 1956, sixteen days after exposure to turkeys subsequently proved to have psittacosis. Approximately nine days previously he had a sudden onset of headache, chills and fever. He was seen by a physician who prescribed tetracycline but the patient did not follow the recommended therapy, apparently because of partial disorientation. The fever and headache persisted; he gradually became more confused and on the day of admission the family noted the appearance of yellow sclerae. There was no history of cough. The patient had been well in the past and had had no history of disease of the heart, lung, liver or kidney.

On examination the patient was found to be acutely ill, semicomatose, dehydrated and icteric. His temperature was 102°F.; pulse 100, respiration 40, blood pressure 130/80 mm. Hg. The nose and throat were normal except for slight increased redness of the pharynx. There was slight nuchal rigidity. There was dullness over the right lower lobe and inspiratory and expiratory sibilant rales were heard in the area. The heart was enlarged to the anterior axillary line and there was a grade 1 systolic murmur. The liver was enlarged to palpation, but the spleen was not felt. The tendon jerks were hypoactive.

The laboratory examinations revealed a red blood

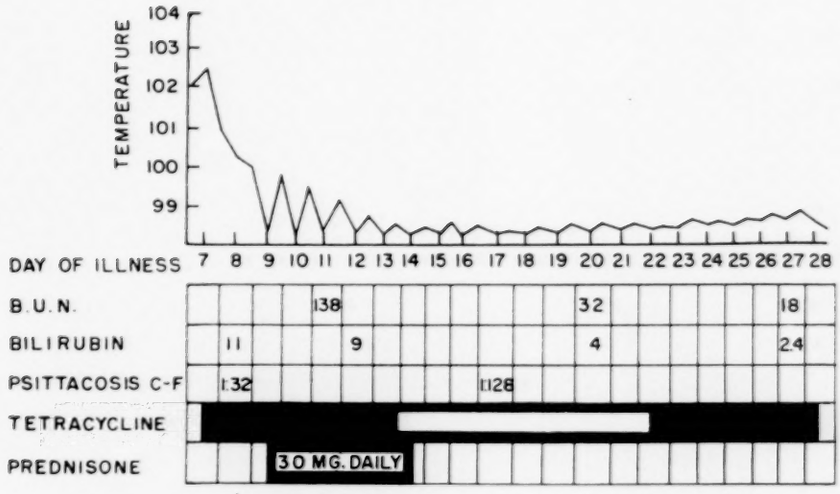


FIG. 6. Case II. The clinical course of a sixty-two year old poultry house worker with psittacosis.

cell count of 4,970,000/cu. mm., hemoglobin 13.2 gm. per cent, hematocrit 46 volumes per cent, white blood cells 6,400 with 72 per cent polymorphonuclear leukocytes and 28 per cent lymphocytes. The urine had a specific gravity of 1.008 with 2-plus albumin, 6 to 8 white blood cells per high power field with an occasional granular cast. The serum bilirubin was 11 mg. per cent; thymol turbidity 21 units, cephalin flocculation test 4-plus in twenty-four hours, prothrombin activity 63 per cent. Blood culture was sterile. Lymphogranuloma venereum complement-fixation reaction was positive in a dilution of 1:32. The serum sodium was 141 mEq./L., and CO_2 15 mEq./L. Roentgenographic examination of the chest on admission revealed haziness in the region of the right lower lobe. The patient was treated with tetracycline, prednisone, oxygen and parenteral fluids. (Fig. 6.) He gradually improved and was discharged on the twenty-first hospital day. Liver function tests returned to normal and he has remained well.

COMMENTS

The relationships of parrots to pneumonitis in human beings was first suspected as early as 1892, although the importance of parakeets in this connection was appreciated only when K. F. Meyer and B. Eddie recognized in 1931 and 1932 the wide distribution of latent psittacosis in the local breeding establishments and aviaries of California [*21*]. In 1929 and 1930 there was an epidemic of approximately 750–800 cases of parakeet psittacosis spread over the United States [*21*]. In 1942 Meyer called attention to the disease in pigeons and chickens, with reports of human infections [*4*]. Wolins [*22*] reported eight cases resulting from contact with the domestic Pekin duck in 1948, and in 1952 Ward and Birge [*23*] reported cases following contact with pheasants. In 1955 Korns [*24*] reported nineteen cases of psittacosis among duck handlers on Long Island, the virus being recovered from 34.5 per cent of ducks examined; 42 per cent of persons handling ducks had positive complement-fixation tests.

Pioneer work in the importance of the turkey as a source of human infection was carried out by Dr. J. V. Irons at the Texas State Department of Health Laboratories, Dr. John P. Delaplane of the Agricultural and Mechanical College of Texas, and Dr. Morris Pollard of the University of Texas Medical Branch at Galveston, and their associates.

The importance of turkey-borne disease in other parts of the country is not known. The epidemic reported in this paper represents the sixth observed in Texas associated with the commercial processing of turkeys.

Psittacosis is usually considered a disease of moderate severity with a fatality rate varying from 10 to 40 per cent in various outbreaks. The cases observed in this outbreak emphasize the wide variation in severity of the disorder. It is likely that the observed sporadic cases represent selected cases of more than usual severity, mild or asymptomatic illnesses remaining unrecognized.

In the fatal case of this series, the autopsy findings may be summarized as follows: (1) bilateral severe interstitial pneumonitis; (2) severe tracheobronchitis; (3) acute segmental "toxic"

nephrosis ("lower nephron nephrosis"); (4) acute non-specific reactive hepatitis; and (5) multiple focal lymphocytic meningitis. Inclusions of coccobacillary bodies similar morphologically to those previously described in psittacosis were observed in the lungs, within the cytoplasm of mononuclear macrophages; none were observed elsewhere.

The occurrence of jaundice in the course of psittacosis has not been previously described as a specific finding nor has the onset of acute anuria heralded death in the reported cases. However, there have been general references to the fact that "icterus occurs only in the exceptional cases" [*25*]. Hegler [*26*] in 1931 reported that icterus was observed in a single fatal case of "biliary pneumonia" in a sixty-five year old woman. No confirmatory laboratory findings were given. Focal changes in the liver have been frequently commented upon.

The jaundice, acute anuria, central nervous system signs and the severity of the pneumonitis in the two cases reported would strongly favor the generalized nature of the psittacosis infection. The failure to respond to tetracycline therapy could be related to the severity of the infecting dose in the patient whose job entailed close contact with large numbers of struggling birds, and the delay in beginning treatment. The pathologic correlation is confused by the clinical features suggesting hypoxia and dehydration, and the relatively mild liver changes described at autopsy. However, it is unlikely that the anoxia played a major role in the jaundice, since the serum bilirubin fell while the pneumonia and anoxia progressed.

The meningeal exudate in this case, although focal in cellular exudate, was similar to that described by Walton of Birmingham, England [*17*] and in the reviews of Polayes and Lederer [*16*] and Sprunt and Berry [*18*]. As in Walton's case, the meninges of the present case contained a soft, moist, gelatinous exudate over the medial portions of the cerebral hemispheres; the exudate contained a rather mild and diffuse infiltration of large tissue macrophages together with focal perivascular collections of lymphocytes and occasional plasma cells. This arachnoiditis must explain the central nervous system signs as no demyelinations or neuronal damage were found. Demyelination has been occasionally described in the brain in cases studied previously [*18*]. No cellular parasitism was discerned in the meninges of the fatal case.

The demonstration of cellular parasitism in the liver and in the meningeal exudate would make us more receptive to the possibility of direct involvement of these areas in the infection. L.C.L. bodies have been demonstrated histologically in secretions from established psittacosis in relatively few cases. Lillie [*27*] described them in the lungs, Binford and Hauser [*12*] have demonstrated them in the liver, Walton [*17*] described them in the meninges, and also recovered virus from the lungs and spleen in one case. One gets the impression that these evidences of cellular parasitism may be found in these organs in a frequency proportionate to the care taken to find them; on the other hand many observers believe that the difficulty is enhanced when the patient has been treated with antibiotics. It is probable then that tetracycline therapy in this case made finding of virus particles more difficult.

The psittacosis virus was isolated from the flock of turkeys involved in the epidemic, but no attempts were made to recover the virus from human infections. It is unfortunate that attempts were not made in the patients with hepatitis, but previous efforts have failed in the Texas epidemics. In turkeys, the administration of tetracycline usually makes recovery of the virus impossible.

SUMMARY

1. Human psittacosis is a disease of increasing importance. It occurs not only sporadically following exposure to psittacine birds, but epidemics are being encountered among poultry workers exposed to chickens, ducks and turkeys.

2. Psittacosis varies in severity from a mild, relatively asymptomatic influenza-like illness to a severe systemic, fatal disease.

3. The clinical features of turkey-borne psittacosis are described as they were observed in an outbreak infecting twenty-four of forty workers.

4. Two of the patients infected in this epidemic exhibited clinical and laboratory evidence of hepatitis with renal decompensation. One of the patients died and autopsy findings revealed a severe interstitial pneumonitis with tracheobronchitis, acute toxic nephrosis, acute non-specific reactive hepatitis, and multiple focal lymphocytic meningitis.

Acknowledgment: We wish to thank Dr. J. V. Irons, Director of Laboratories, Texas State

Department of Health, for his advice and cooperation in performing the complement-fixation tests in the patients reported in this paper. Dr. Karl F. Meyer was kind enough to allow us to review reprints from his papers appearing in the early German literature.

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Seminar on Mycotic Infections

North American Blastomycosis*

E. Richard Harrell, M.D. *and* Arthur C. Curtis, M.D.
Ann Arbor, Michigan

Since 1894, when Gilchrist [*1,2*] described the microscopic appearance of the causative organism of North American blastomycosis at a meeting of the American Dermatological Association, a gradual understanding of the nature of this systemic mycosis has evolved. The credit for this advance belongs to many, but notably to the Duke Medical School group. D. T. Smith, Conant, Martin, Baker, and more recently J. G. Smith [*3–16*] have contributed greatly to our fundamental knowledge of the disease. Originally there was great confusion in the identification of the causative organism and its cultural requirements [*4,17,18*], but there now is agreement that its proper name is Blastomyces dermatitidis, and the characteristics of this organism in both tissue and culture have been universally accepted.

During recent years the clinical course of the disease has been delineated more clearly, particularly by Schwarz and Baum [*19*] and by Wilson [*20,21*]. The concept that this fungus disease, like coccidioidomycosis and histoplasmosis, is acquired as a primary pulmonary infection and that the cutaneous form, which is acquired by primary inoculation, is an extreme rarity, has yet to be completely accepted by all investigators and clinicians interested in mycology [*22*]. There is mounting evidence that a subclinical pulmonary form of the disease exists [*11,23*]. This lends added support to the concept of the clinical disease advanced by Schwarz and Baum.

Important changes in the therapy of North American blastomycosis have occurred within the past ten years. The use of the aromatic diamidines—stilbamidine, 2-hydroxystilbamidine and amino-stilbamidine—in the therapy of this disease did much to reawaken interest in the disorder. Amphotericin B promises to be an even more effective therapeutic agent [*24,25*]. We would like to document a follow-up of patients with systemic North American blastomycosis who were originally treated with Amphotericin B [*24*], and also to add four other cases to this series of patients. Several excellent review articles on North American blastomycosis are available in the medical literature [*3,17,19,23,26,27*].

Geographic Distribution

With the increase in foreign travel by residents of the North American continent it is inevitable that increasing numbers of cases of North American blastomycosis will be reported from countries throughout the world [*28–36*]. However, there is still great doubt that the organism is indigenous to any area of the world other than the North American continent. Many instances of the disease have been recognized in Canada [*17,37–39*] but the majority of patients infected with B. dermatitides have originated from the South, Southeastern and mid-Western areas of the United States. Martin and Smith [*3*] were the first to attempt to map the geographic distribution of North American blastomycosis within the United States. Their review of the acceptable reported cases from the world literature found 98 per cent of the cases originating from the United States. Illinois and Louisiana were the two states with the largest number of cases. Schwarz and Goldman [*40*] studied the incidence and distribution of North American blastomycosis by means of questionnaire; they described 101 patients with the disease who were seen or treated by dermatologists or thoracic surgeons during the first six months of 1953. The majority of these cases were found in Central and Southeastern United States, the largest number from the State of Wisconsin; this latter finding is borne out by the

* From the Department of Dermatology, University of Michigan Medical Center, and the V. A. Hospital, Ann Arbor, Michigan.

large numbers of cases reported from the Mayo Clinic [*23*] and from the Milwaukee County General Hospital [*27*].

EPIDEMIOLOGY

The exact mode of infection of B. dermatitides remains to be delineated. The causative organism has been strangely elusive to all attempts to isolate it from the soil in which it must exist. While the blastomycetes have been grown in soil specimens in the laboratory [*41,42*] and have also been grown on specimens of bark experimentally [*43*], attempts at isolation from specimens of soil taken from areas in which infected persons have lived have been consistently negative [*11*]. There have been many suggestions as to a natural source of the organism [*44–46*]; however, all such reports will remain nothing more than suggestions until the cultural requirements from natural sources are determined. Neither has an adequate reservoir of natural infection in animals been established. The only two animals in which the disease has been found to occur as a natural infection are dogs [*47–49*] and horses [*50*].

Two reports of small epidemics of North American blastomycosis have been recorded [*11,51*]. The authenticity of the report by Bonoff [*51*] of twenty-three cases of pulmonary blastomycosis occurring in Okinawa has been rightfully questioned [*23,52*], since identification of the blastomycetes was made by direct microscopic examination of sputum, and cultural confirmation was lacking.

The most important development in recent years in the epidemiology of North American blastomycosis is the well documented report of eleven cases of North American blastomycosis occurring in Grifton, North Carolina [*11*] and the follow-up studies made in this endemic area [*12,13*]. It is unfortunate, however, that even these studies were unable to pinpoint the source of infection more precisely.

CLINICAL CHARACTERISTICS

Age, Sex, Race, Occupational and Seasonal Incidence. The disease has been recorded in most of the races inhabiting the North American continent. There is, however, a definite apparent preference of the organism for the male sex. Reported ratios of men to women range from 4.3:1 to 15:1 [*3,13,23*]. Those in the age group of fifty to seventy years are most commonly found to have this fungus disease [*23*]. However, seven of the eleven patients recorded in the epidemic by Smith were under sixteen years of age. It is of great interest that two of these eleven patients were siblings. This is the first acceptable [*11,53*] instance of the disease in siblings. North American blastomycosis has also been recorded in the pregnant female [*54,55*].

There is no apparent occupation which predisposes to the development of North American blastomycosis. The statement that this disease occurs most commonly in the agricultural worker is true only of those reports emanating from agricultural areas. In the Detroit, Michigan, area the disease is found to be most common in automobile workers.

It has been stated that North American blastomycosis has a seasonal incidence. Martin [*14*] reports that the disease occurs more commonly in the winter months, and Smith [*11*] corroborates this statement with an analysis of the cases reported in the North Carolina epidemic. One cannot help but wonder, however, how much time might elapse between acquisition of the infection and the development of clinical lesions or symptoms.

CLASSIFICATION

From 1902, when Walker and the Montgomery [*56*] reported the first case of systemic infection of blastomycosis, until 1951 it was generally considered that North American blastomycosis could be divided into cutaneous and systemic forms. The cutaneous form was characterized by the development of granulomatous skin lesions, often multiple, and usually over an exposed area of the body. It was thought that generalized systemic involvement could occur by dissemination of the organisms from these cutaneous lesions. In contrast, the systemic or disseminated form of the disease was thought to occur by pulmonary inhalation, and that the blastomycetes could then be disseminated to skin, subcutaneous tissue, bone or other systems of the body [*10*]. Since the time that Schwarz and Baum advocated a change in this concept [*19*] there has been mounting evidence for revision of the classification of North American blastomycosis into (1) primary cutaneous inoculation blastomycosis and (2) systemic blastomycosis. We are in full agreement with this classification.

Primary Cutaneous Inoculation Blastomycosis. The clinical features of this form of the disease follow rather closely those which have been well documented in coccidioidomycosis, sporotricho-

sis and histoplasmosis [*20,57*]. Within a period of one to four weeks following inoculation of the B. dermatidis organism into the skin, a relatively painless nodule develops. This slowly assumes the character of a granulomatous, chancriform lesion, which closely resembles primary inoculation tuberculosis or sporotrichosis. Satellite lymphadenopathy next develops, as may multiple nodules along the lymphatic channels [*20*] similar to those which so classically occur in sporotrichosis. In all probability, North American blastomycosis acquired by this particular inoculation route develops into a much more benign type of disease process than that acquired by inhalation. There have been no recorded reports of generalized dissemination of the organism following this type of known primary inoculation. Wilson et al. [*20*] record four cases of such known primary inoculation blastomycosis. Three of these occurred in physicians who accidentally inoculated a finger or hand during autopsy, and the fourth in a mortuary attendant who accidentally sustained a needle puncture preparing a patient who had died of North American blastomycosis. All these patients recovered without evidence of systemic disease.

We had occasion to see a similar type of known primary inoculation North American blastomycosis when a twenty-five year old white, male graduate student in bacteriology accidentally inoculated his index finger when he sustained a cut while picking up the pieces of a broken tube of a viable 37° culture of B. dermatitidis. At the time of the injury it was thought that inoculation may have occurred. Some twelve to fourteen days following the inoculation a slightly erythematous, non-tender area of induration developed at the site of the healed laceration. This gradually increased in size to approximately 6 mm., at which time the lesion was completely excised surgically. B. dermatitidis was isolated on culture of the excised specimen, and the single budding organisms were also seen on pathologic examination of the tissue. This infection apparently had not existed for a long enough period of time for epitrochlear or axillary lymphodenopathy to develop. The blastomycin skin test did not become positive, nor were complement fixing antibodies demonstrable. This infection occurred in 1953. There has been no evidence of any systemic disease or localized recurrence since that time.

Scott [*58*] recorded what seems to be an acceptable instance of primary inoculation blastomycosis following a dog bite of the index finger. This case is particularly interesting since the dog was being examined by a veterinarian for an unexplained illness at the time the bite was sustained. No mention is made of the presence or absence of satellite lymphadenopathy in this report. The patient responded promptly to the administration of iodides and superficial x-ray therapy, and has apparently remained free of any other evidence of the infection. It also seems entirely possible that a case reported by Macaulay [*22*] of a verrucous, granulomatous lesion of the toe following a blister might represent an instance of primary inoculation cutaneous blastomycosis. However, it must be borne in mind that there is a definite propensity for cutaneous lesions to develop by hematogenous spread from other foci following trauma to the skin. This would explain to some extent the confusion in the classification of North American blastomycosis which has existed in the past.

Systemic Blastomycosis. In spite of the fact that B. dermatitidis has not yet been cultured from the soil, it seems probable that the disseminated form of the disease begins as a primary pulmonary infection by inhalation of the causative agent. Definite subclinical pulmonary blastomycosis has now been documented [*11,13*], and it seems reasonable that this form of the disease may be more prevalent throughout the endemic areas of the North American continent than is appreciated. When symptoms do occur following infection of the lungs, it is common for the patient to experience a low grade febrile reaction, vague chest pains, night sweats and cough productive of sputum which, as the disease progresses, may be bloodstreaked. The symptoms are almost identical with those of early pulmonary tuberculosis. Erythema nodosum has been reported as an accompaniment of this form of the disease [*11*]. It is not unusual for the pulmonary symptoms gradually to subside, and for the patient to remain almost if not completely asymptomatic until cutaneous granulomas develop. Dissemination to the skin occurs primarily through hematogenous routes. Reports of blood cultures positive for B. dermatitidis have been recorded [*19,59*]. The cutaneous lesions often first have the appearance of benign looking papulopustular nodules. However, these nodules may enlarge with alarming rapidity by direct peripheral extension, forming elevated, erythematous, exuberant, verrucous, ulcerating

granulomas. Greatest activity of the lesion is usually in evidence at the advancing peripheral border, and the line of demarcation between involved and uninvolved skin is sharp. One frequently sees a tendency for spontaneous healing to develop in the central portion of the lesions. (Fig. 1.) At times, such cutaneous lesions can reach tremendous proportions, and cover large areas of the skin. While such lesions are characteristically found in North American blastomycosis, they may also occur in the cutaneous granulomas found in coccidioidomycosis, sporotrichosis, cryptococcosis and, less frequently, histoplasmosis. Other diseases to be included in this differential diagnosis are tuberculosis, verrucosa cutis, tertiary syphilis, cutaneous neoplasm, drug eruptions, leishmaniasis, lymphoma, granuloma inguinale and pyoderma vegetans. It is therefore a mistake to rely solely on the appearance of the cutaneous lesions for diagnosis. The subcutaneous tissue is also a favorite target for the hematogenously spread blastomycetes, and subcutaneous nodules, abscesses and draining sinus tracts are not infrequently found in association with the verrucous, cutaneous granulomas. Next to the skin and subcutaneous tissue, the most common structure involved is the osseous system [*3,10,23*]. Sharply demarcated destructive lesions are found in the ribs and vertebrae, less commonly in the long bones, the skull, the knee and elbow joints. Involvement of the joints produces a septic type of arthritis.

Not enough attention has been directed toward blastomycosis of the genitourinary tract. We have had occasion to observe prostatic abscesses and epididymitis. Kunkel [*23*] also emphasizes the importance of blastomycosis of the genitourinary tract, as do Schwarz and Baum [*19*]. The latter authors document their findings in eleven patients, who exhibited evidence of blastomycosis of the genitourinary tract, with involvement of the kidney, prostate, testes, epididymis, seminal vesicles and bladder. Renal casts composed solely of B. dermatitides have also been reported, once in a patient in whom a rapidly terminating septicemia developed due to B. dermatitidis [*39*].

Blastomycotic involvement of other systems of the body may occur. The central nervous system is not immune. For undetermined reasons, the gastrointestinal tract remains the most resistant to such infection.

The original pulmonary focus of infection may



FIG. 1. A peripherally enlarging exuberant blastomycotic granuloma of the back. This lesion exhibits the characteristic sharply defined elevated border and tendency for spontaneous central healing.

be quite insignificant in its appearance on roentgen examination or in the production of clinical signs or symptoms. This has been well documented, and does much to explain the confusion which has occurred in the clinical classification of this disease. We have had occasion to record such a patient [*60*], and Schwarz and Baum [*19*] have described pulmonary healing despite widespread dissemination of the disease. Advancing pulmonary blastomycosis does not seem to follow any set pattern. The x-ray picture of massive bilateral pneumonia has been recorded [*11*]. A form of military pneumonitis has also been described [*10*]. However, more commonly the pulmonary process confines itself to infiltration of fibrous tissue without cavitation [*23*]. When cavitation does occur, it is unusual to find fluid levels within the cavities.

IMMUNOLOGY

The immunologic aspects of North American blastomycosis have been re-evaluated recently by Wilson [*21*]. D. T. Smith [*8*] found that the prognosis is best in those patients who have posi-

tive blastomycin skin tests and in whom serum complement fixing antibodies fail to develop, and poorest in those in whom the skin tests are negative and the complement fixing antibody titers are high. We have found this correlation to be useful in evaluating the results of the therapy we have employed [*60*]. In our own patients who have had advancing systemic North American blastomycosis, the blastomycin skin test has usually been negative. A negative blastomycin skin test does not exclude this disease.

The blastomycin skin testing antigen may be of two basic types. The type most commonly employed is obtained as a filtrate of 37 degrees yeast phase culture of B. dermatitidis, grown on either a solid or a liquid medium [*61,62*]. Specificity of antigen so obtained is high, and shows less tendency for cross reaction with the skin test for histoplasmosis. The antigen is a polysaccharide which is relatively protein-free. The second type of antigen is a suspension of the heat-killed 37 degrees B. dermatitidis grown on either a solid or a liquid medium. The treated fractions containing protein show much greater tendency to cross react [*62,63*] than those which are largely polysaccharide. The first mass skin test survey using blastomycin antigen was performed by Martin [*14*] on 972 patients in a North Carolina State Mental Hospital. Only fifteen of these patients reacted to the blastomycin antigen, and it was found that thirteen of these fifteen patients were also histoplasmin-positive reactors. Furcolow et al. [*64*] reported the results of his experience in skin testing 7,194 school children in the Cincinnati, Ohio, area. They found 12 per cent of this group to have a positive reaction to the blastomycin skin test, but only one of the positive group was negative to the histoplasmin skin testing material indicating probable cross reactivity. J. G. Smith et al. [*12*], in a study of the endemic area of North American blastomycosis in North Carolina, performed tuberculin, histoplasmin and blastomycin skin tests, and also obtained complement fixation titers and chest roentgenograms. In all, 1,648 persons were surveyed. Only 2.9 per cent of this group were blastomycin-sensitive, while 6.4 per cent were histoplasmin-sensitive. Of the 2.9 per cent of persons who were blastomycin positive, 4.7 per cent were found to have positive blastomycin complement fixation titers. Some two years later forty-three of the eighty-three persons with positive reactions to the blastomycin skin test were rechecked. It is interesting that 34.8 per cent of those who had previously had a positive blastomycin skin test reverted to complete negativity during this two-year period. Of the group exhibiting positive complement fixing antibody titers 91 per cent had also reverted to negativity during this interval. None of those with a negative reaction to the blastomycin skin test was found to have become positive. Harris et al. [*13*], in further analyzing the skin reactivity of the population of this endemic area, found that the correlation between blastomycin and histoplasmin sensitivity in the survey indicated that antigens common to blastomycin and histoplasmin would not explain completely "the unexpectedly greater number of individuals who were sensitive to both histoplasmin and blastomycin. The evidence may implicate a common mode of contact with the agent causing sensitivity to these two materials."

By comparison with histoplasmosis and coccidioidomycosis, North American blastomycosis causes rather low complement fixing antibody titers. It has been unusual in our experience to find complement fixing antibody titers in this disease greater than 1:128; more commonly titers of 1:16 to 1:32 are found. Wilson has emphasized that the presence of complement fixing antibodies in no way indicates immunologic resistance, but if anything is indicative of the number of proliferating infecting organisms at the time the specimen is secured [*21*].

DIAGNOSIS

A diagnosis of North American blastomycosis can be established definitively only by culturing the causative organism on the proper medium. Less certain identification can be made by finding the blastomycetes on direct microscopic examination or in pathologic specimens. It is a mistake to rely solely on clinical judgment, and too much reliance should not be placed on the blastomycin skin test.

Direct Examination. The fresh clinical material to be examined, whether it be pus taken from a cutaneous lesion or a draining sinus, or sputum, urine or biopsy tissue, should be placed on a glass slide and mixed with a drop of 15 per cent potassium hydroxide solution. This preparation is then heated gently over a flame and examined under a microscope using as low a condenser light as possible. This enables the observer to see the refractile wall of the single budding

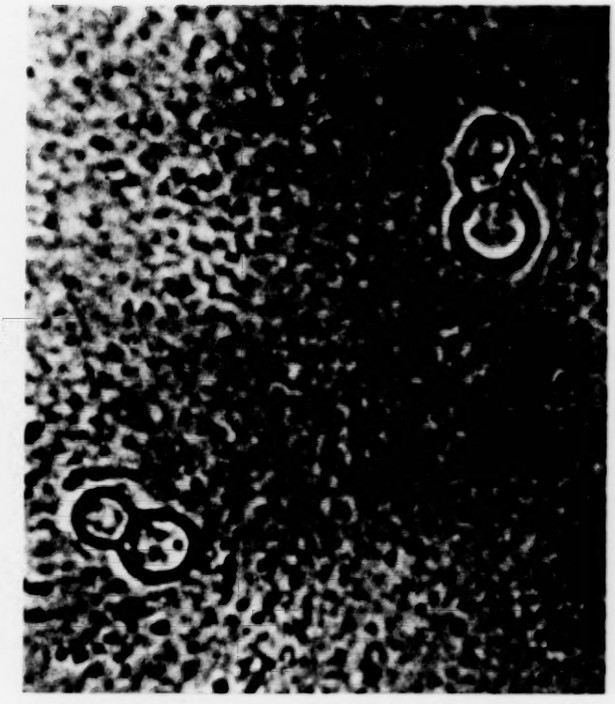


FIG. 2. Appearance of the single-budding B. dermatitidis in direct microscopic examination of pus taken from a cutaneous lesion.



FIG. 3. Unusual pattern of growth exhibited by B. dermatitidis in the sputum of a patient in whom relapse occurred following amphotericin B therapy.

blastomycetes most clearly and to distinguish the characteristic architecture of the budding cells from oil droplets and other artifacts. (Fig. 2.) It is usually possible to see the structures, which measure 5 to 15 μ. in diameter, under low power. In one of our patients treated with amphotericin B in whom relapse occurred following therapy we have had occasion to find structures in the sputum which deviated from the expected single-budding appearance, assuming what appeared to be almost an abortive attempt at hyphal production. (Fig. 3.) The best opportunity for demonstration of the causative organisms on direct microscopic examination lies in procuring a tiny droplet of pus obtained by gentle pressure from the edge of an expanding cutaneous lesion.

Cultures. The suspected infected clinical material should be cultured on Sabouraud's glucose-agar at room temperature, as well as on blood-agar or beef infusion-dextrose-agar at 37°C. Bacterial contamination can be almost completely controlled by the addition of 0.5 mg. of chloramphenicol per milliliter of agar. It is also desirable to add 0.5 mg. of cyclohexamide per milliliter of agar to discourage the growth of fungal contaminants. These two latter substances are routinely added to all of our agar slants during the routine preparation of the culture tubes. Growth of B. dermatitidis usually becomes visible on the room temperature slant within ten to fourteen days from the time the preparation was inoculated. In its early stages of growth at room temperature the organism may develop aerial spikes which have been referred to as coremia. These soon flatten out, and the slow-growing whitish to brownish filamentous growth gradually covers the surface of the agar slant. Not uncommonly, this room temperature pattern of growth produces a concentrically ringed appearance. Examination of the room temperature colony enables one to see many raquet cells and branching hyphae bearing a small microconidium. None but the most experienced mycologists are able to make a positive cultural identification from the room temperature colony. The 37°C. culture grows more slowly and develops into a waxy, wrinkled, white to brownish white, yeast-like culture which, upon microscopic examination, reveals the single budding, thick-walled blastomycetes which were seen on direct microscopic examination of infected material. In addition to the single-budding organisms, short, abortive hyphal elements are also encountered.

Animal Inoculation. Both guinea pigs and mice are susceptible to the development of systemic North American blastomycosis when inoculated intraperitoneally with infected clinical material. The disease will also develop in these animals when they are inoculated with suspen-

sions of either the room temperature or 37°c. yeast culture of B. dermatitidis. When inoculated with the yeast phase culture, laboratory animals have a rapidly fatal illness from which one can recover the causative agents with relative ease.

Biopsy. In many respects the biopsy specimen taken from a cutaneous lesion of North American blastomycosis presents a fairly characteristic pathologic picture. There is very marked proliferation of the epidermal prickle cells, developing extreme acanthosis of a degree not often seen in any other infectious disease [*21*]. Below this exaggerated acanthosis there is usually a dense, granulomatous infiltrate consisting of lymphocytes, polymorphonuclear leukocytes, eosinophils and epithelioid cells, some of the latter having formed Langerhans' type of giant cells. Within the proliferation of the prickle cells there are characteristic microabscesses, composed of large numbers of polymorphonuclear leukocytes, lymphocytes and eosinophils. It is in this area that the B. dermatitidis organisms are most likely to be found. They appear as round, budding structures, some apparently empty, others with visible protoplasm shrunken away from the refractile wall, giving a double contoured appearance. It is difficult, yet possible, to make absolute identification of this disease process on the basis of the microscopic appearance of a single budding blastomycete in tissue. Exceedingly small blastomycetes, measuring 2 to 4 μ in diameter, have been described by several authors [*65–67*]. These have occurred in tissue specimens and have been found in association with the typical larger sized organisms. It is often of help to use the periodic acid-Schiff staining method to demonstrate B. dermatitidis organisms in pathologic tissue if difficulty is encountered in finding them in the routinely stained slides [*60*].

THERAPY

A great many therapeutic agents were advocated in the treatment of North American blastomycosis prior to the use of the aromatic diamidines in 1950 [*67,70*]. The principal agent employed up to 1950 was potassium iodide administered as a saturated solution orally, or sodium iodide administered intravenously. Much emphasis was placed on the presence or absence of cutaneous hypersensitivity of the patient to blastomycin skin testing. The Duke University group [*10*] advocated desensitization with blastomycin prior to iodide therapy, if the blastomycin skin test was positive. There can be no question that the iodides did apparently exert some beneficial influence in many patients with this disease; however, such therapy was rarely curative. It is interesting to note that in most of the patients cured by iodide therapy, the immunologic status of the patient was characterized by a positive blastomycin skin test and absent complement fixing antibody. Cornbleet [*71*] more recently has advocated the use of a saturated solution of potassium iodide combined with thyroid extract. He reports impressive results in nine patients treated in this manner. He also records "near disastrous results" when propylthiouracil was administered to a patient instead of thyroid extract. He postulates that B. dermatitidis acts as a goitrogenic agent. Unfortunately, he does not mention the immunologic status of any of the nine patients reported.

We believe that there is no longer a place for roentgenotherapy in North American blastomycosis. Judicious cauterization with or without curettage may still be useful for local removal of cutaneous blastomycotic lesions; however, this should be done with the realization that the patient has systemic disease with dissemination of the organism to the skin to produce these cutaneous lesions. Surgical resection of pulmonary lesions will undoubtedly continue. Kunkel [*23*] outlines the criteria for surgical intervention in North American blastomycosis. These criteria include positive identification of the disease by culture or direct microscopic examination, no evidence of dissemination from a pulmonary focus, and limitation of the process to one lung. He also stated that the disease should be of at least two months duration. We believe that pulmonary cavitation may also be an indication for surgical intervention. However, in our opinion an adequate trial of chemotherapy with amphotericin B should be made before any surgical procedure is undertaken; and if resection is carried out, it should be performed under coverage of chemotherapy [*72*].

Following reports by Colbert et al. and Schoenbach and his associates, a great many case reports have appeared in the literature attesting to the efficacy of the aromatic diamidines in the treatment of North American blastomycosis [*11,23,32,60,73–92*]. Some of these reports record recurrences following the administration of massive amounts of stilbamidine, 2-hydroxystilbamidine and aminostilbamidine

[*26,60,93*]. We will make no attempt to review the details of the pharmacology or mode of action or administration of the aromatic diamidines, since this has been described in detail elsewhere [*77,94,95*]. 2-Hydroxystilbamidine has proved to be less toxic than stilbamidine. This drug, in a dosage of 0.450 mg. per dose, can be slowly administered intravenously without great risk to the patient, and without significant unpleasant side effects. We believe that 2-hydroxystilbamidine is capable of curing systemic North American blastomycosis when the infected person can marshal an adequate immunologic defense, as evidenced by a positive blastomycin skin test and negative complement fixing antibody. Our therapeutic failures using the aromatic diamidines have occurred almost exclusively in patients who failed to exhibit cutaneous blastomycin sensitivity and who also had significantly positive complement fixing antibody titers. Many of the patients in whom 2-hydroxystilbamidine has been reported to be extremely effective have had a very mild form of the disease. It is this type of patient that probably would have shown some response to potassium iodide therapy.

Amphotericin B Therapy. Gold et al. [*96*] in 1955 reported the isolation of amphotericins A and B from an unidentified species of streptomyces obtained from a soil specimen taken from near the Orinoco river in Venezuela. Vandeputte [*97*] et al. at the same time reported on the purification and separation of amphotericins A and B. *In vitro* studies have shown that as little as 0.5 μg. per ml. of medium is sufficient to inhibit growth of B. dermatitidis completely [*98*]. Since these reports, there have been many articles recording the beneficial effect of intravenously administered amphotericin B in deep mycoses [*24,25,99–112*]. These articles report favorable effects in North American blastomycosis, cryptococcosis, histoplasmosis and coccidioidomycosis. A recent report [*109*] records in detail the physical, chemical and biological properties, the *in vitro* spectrum and mode of action, the acute and chronic animal toxicity, absorption and excretion in animals and experimental animal infections. This report also records in detail the procedure for bioassay of amphotericin B in body fluids, as does the report by McNall et al. [*113*].

Only 3 reports record the use of amphotericin B in the treatment of systemic North American blastomycosis [*24,25,114*]. We recorded details of four cases of severe, stilbamidine-resistant North American blastomycosis treated with amphotericin B intravenously. Derbes and Krafchuk [*114*] described a patient with North American blastomycosis with pulmonary lesions, granulomatous lesions of the face and oral mucous membranes, a negative blastomycin skin test and complement fixing antibody titers which varied from 1:8 to 1:32. This patient was treated with amphotericin B, administered orally, in amounts of 3.0 gm. per day for three months; the drug was not given intravenously. Single budding organisms were found in the tissue on serial biopsy after the cutaneous granulomas had clinically healed. Unfortunately, the authors make no mention of culture of these organisms. The report by Utz et al. [*25*] on the use of amphotericin B in North American blastomycosis would tend to discount the effectiveness of amphotericin administered orally. One of the two patients with systemic blastomycoses reported by Utz was treated with 5 gm. of amphotericin B per day given orally for twenty-eight days, with no apparent change. When this patient was treated with relatively small doses of amphotericin B administered intravenously the sputum became culturally and microscopically negative for blastomycetes. The second patient with North American blastomycosis described by Utz was treated only with intravenously administered amphotericin B. Objective improvement was reported after 115 days of therapy.

Follow-up studies of our four original patients treated with amphotericin B (Cases I through IV) and four additional similarly treated persons are summarized in Tables I and II.

CASE REPORTS

CASE I. C. R. is a fifty year old white male automobile factory worker from Detroit, Michigan, whose first indication of North American blastomycosis was an ulcerating lesion of the mouth noted in May 1953. Multiple cutaneous granulomas of the face and neck then developed. Roentgenograms of the chest revealed irregular parenchymal densities in the right anterior first inner space. (The patient had no pulmonary symptoms.) Sputum examinations were negative; however, a gastric analysis in December 1956, revealed B. dermatitidis on culture. This man had received a total of 25.4 gm. of stilbamidine and 2-hydroxystilbamidine, yet relapse occurred and he gave evidence of active disease. He was initially treated with amphotericin B in December 1956, at which time he received a total of 0.5 gm. This was administered by slow intravenous drip over a period of

TABLE I
CLINICAL SUMMARY

Case No.	Patient, Age (yr.) and Sex	Race	Occupation	Duration of Disease (yr.)	System Involvement	Blastomycin Skin Test	Complement Fixation Test	Previous Diamidine Therapy (gm.)
I	C. R., 50, M	W	Automobile worker	4	Lungs, skin	0	1–5	25.4
II	E. I., 39, M	W	Automobile worker	13	Lungs, skin, bone	0	1–80	27.0
III	H. J., 24, M	N	Automobile worker	5	Lungs, skin, subcutaneous abscess, psoas abscess, bone and prostate	0	1–64	39.6
IV	G. G., 44, M	N	Laborer	9	Lungs, skin, subcutaneous abscess, bone and prostate	0	1–64	48.0
V	H. G., 56, M	W	Farmer	4	Lungs, skin	0	0	46.0
VI	W. J., 69, M	W	Carpenter	$^{5}/_{12}$	Lungs(?), skin	0	1–4	0
VII	E. M., 41, M	W	Laborer	$^{9}/_{12}$	Lungs, skin	0	0	0
VIII	M. A., 33, M	W	Physician	$^{6}/_{12}$	Lungs	0	0	0

six to eight hours. The drug was suspended in 1,000 cc. of 5 per cent dextrose in water. Because of the toxicity, which was manifested by a febrile reaction, nausea, vomiting and anorexia, the 0.5 gm. total dosage was administered over a period of approximately one month's time. At the end of this time the patient was clinically and bacteriologically well. However, he returned to the hospital three months following discharge, exhibiting new facial granulomas. A second course of 1.0 gm. of amphotericin B was administered in a dosage of 50 mg. per day for twenty consecutive days. The untoward effects of the intravenously administered amphotericin B were minimized by the concomitant use of 10 mg. of prednisolone and 50 mg. of chlorpromazine. No renal toxicity was noted during the administration of either course of amphotericin B. Since the patient was last treated, some twenty-six months ago, he has given no indication of recurrence of his disease and has continued to work. This patient's original blastomycin skin test and all of those performed subsequently have been negative. The weak complement fixing antibody titer (1 : 5) which was present prior to the amphotericin B therapy has reverted to negative.

TABLE II
SUMMARY OF AMPHOTERICIN B THERAPY

Case No.	Patient	Average Daily Intravenous Dose (mg.)	Total Dose (gm.)	Toxic Effects	Time Since Last Treated (mo.)	Present Clinical Result
I	C. R.	50	1.5	Fever, nausea, emesis, anorexia	26	Apparent cure
II	E. I.	50–75	1.0	Fever, nausea, emesis	29	Apparent cure
III	H. J.	50–100	4.0	Substernal pain, dyspnea fever, chills, emesis, anorexia	15	Doubtful
IV	G. G.	50–100	4.54	Fever, nausea, emesis, chills, malaise	14	Doubtful
V	H. G.	50	1.0	Fever, nausea, emesis, malaise	26	Apparent cure
VI	W. J.	50	1.0	Mild nausea only	26	Apparent cure
VII	E. M.	50	1.0	None	18	Apparent cure
VIII	M. A.	50	1.0	Fever, nausea, emesis, azotemia, malaise, phlebitis	11	Apparent cure

CASE II. E. I. is a thirty-nine year old white male automobile factory worker in whom signs and symptoms of this disease developed in December 1944. He was first seen at the University of Michigan Medical Center in Ann Arbor, Michigan, in February 1945, at which time a diagnosis of North American blastomycosis was established. This patient has had extensive pulmonary, cutaneous and osseous involvement throughout the thirteen-year course of his disease. Administration of 27 gm. of the aromatic diamidines did not effect a cure. Therapy with amphotericin B was begun in January 1957, with a daily dose of 50 to 75 mg. per day, administered intravenously in 1,000 cc. of 5 per cent dextrose in water. A total dose of 1.0 gm. was given over a period of thirty days. Fever and nausea were the only two complaints during administration of the antibiotic, and these reactions were relatively well controlled by the administration of chlorpromazine. The cutaneous lesions healed quite rapidly during the thirty-day period of treatment. The roentgenograms of the chest have also shown improvement. The patient's osseous involvement had apparently healed previous to the amphotericin B therapy. This patient has been readmitted to the University Hospital on two occasions since he was treated with amphotericin B for reconstructive plastic surgery of the face. This has been necessitated by the extensive damage to the eyelids and the nose caused by the cutaneous blastomycotic granulomas. The patient's skin test has always been negative. His complement fixing antibody titer prior to amphotericin B therapy was positive in the relatively high titer of 1:80. Within six months from the time that this patient was started on amphotericin B therapy, his complement fixation titer became negative and has remained negative to date. At the present time, the patient is actively working, and free of any evidence of activity of his disease.

CASE III. H. J. is a twenty-four year old Negro male automobile worker with North American blastomycosis of five years' duration. The onset was heralded by signs of moderately severe respiratory infection in the summer of 1952. Several months later verrucous cutaneous lesions appeared over the face and lower extremities. Six months later a draining abscess of the mandible developed. It was at this time that the diagnosis of North American blastomycosis was established, and stilbamidine therapy was begun. He was given a total of 39.6 gm. of aromatic diamidines between April 1953 and December 1956. In spite of the temporary beneficial effect produced by the administration of these drugs the patient continued to have advancing disease of the lungs, skin, subcutaneous tissue and bone. He also had a large dissecting psoas abscess and a deep draining sinus tract connecting a perivertebral abscess. Amphotericin B therapy was begun in January 1957, the drug being administered intravenously in a daily dosage of 50 to 100 mg. suspended in 1,000 cc. of 5 per cent dextrose and water. Within minutes following the administration of the first dose of amphotericin B chills, fever, tachycardia, dyspnea and severe substernal chest pain developed. Administration of the drug was immediately discontinued and the symptoms disappeared within several hours. Electrocardiograms taken after the episode of chest pain and two days later were normal. Administration of the drug was resumed two days later, and except for development of nausea, vomiting and fever it was well tolerated. By the time 1.0 gm. had been given the draining sinus tract had completely healed, the productive cough had ceased, and all cutaneous lesions showed complete regression. During the ensuing five months the patient gained 17 pounds in weight. However, he was readmitted to the University Hospital on April 6, 1957, with severe left-sided abdominal pain with radiation to the left testicle and a temperature of 104°F. Surgical exploration of the abdomen was performed on April 13, 1957. Numerous loculations were encountered in the region of the old psoas abscess. However, no active granulomatous tissue was found, and the blastomycetes were not demonstrated by direct examination or culture. It was thought advisable to administer amphotericin B prior to the exploratory surgical procedure, in dosage ranging from 75 to 100 mg. every other day. He tolerated the dosage of 100 mg. per day with no more evidence of toxicity than was noted during the dosage of 50 mg., i.e., chills, fever, nausea and vomiting. The drug seemed to be tolerated better when given every other day than on consecutive days. Following discharge the patient remained well and symptom-free; however, during a routine check-up in March 1958, the patient was found to have occasional B. dermatitidis organisms in the sputum, and he was given a third course of amphotericin B, again in doses of 75 to 100 mg. per day, administered on alternate days, for a total dosage of 1.0 gm. Nausea, vomiting, fever and anorexia developed again during the administration of this course. He has had no further therapy since April 1958. He has remained well, without signs or symptoms of activity. The small amount of sputum which is raised has been negative for blastomycetes. This patient's blastomycin skin test has been consistently negative. His initial pretreatment complement fixation titer was 1:64. The titer in September 1957, eight months after treatment was initially started, was 1:16. All three complement fixing tests since that time have been anticomplementary.

CASE IV. G. G. is a forty-four year old Negro male laborer in whom signs and symptoms of "pulmonary tuberculosis" developed in May 1948. The mycotic nature of his pulmonary illness was recognized, and the patient was referred to the University of Michigan Medical Center Hospital, Ann Arbor, Michigan, for treatment in June 1948. Since his initial admission to the hospital many cutaneous granulomas, sub-

cutaneous abscesses, destructive lesions of the ribs, left humerus and vertebra, prostatic abscess necessitating a transurethral resection, and progressive, extensive cavitary pulmonary disease have developed. During his many hospitalizations the patient was given a total of 24.3 gm. of stilbamidine and 23.7 gm. of 2-hydroxystilbamidine. In spite of this vigorous therapy there was progression of his pulmonary and cutaneous lesions. Administration of amphotericin B was begun in January 1957, in the dosage of 50 mg. per day, given at as frequent intervals as the patient would tolerate. After the third dose the patient complained so bitterly of nausea, vomiting and malaise that it was necessary to allow him a two-week's rest before resuming therapy. Prednisolone, 15 mg. per day, and chlorpromazine, 50 mg. per day, were then administered with the antibiotic. The patient then tolerated the amphotericin B therapy in a dosage of 50 mg. per day in 5 per cent glucose in water without significant complaint. The total dose of 1 gm. of the drug was completed by January 31, 1957. The patient was readmitted in May 1957, for a course of 1.5 gm. of amphotericin B. This was necessitated by the finding of blastomycetes in the sputum. This course of the drug was given in a dosage of 75 to 100 mg. per day. Readmission was again necessary in November 1957 because of positive smears and cultures obtained from sputum specimens. This third course of amphotericin B was discontinued when a dosage of 0.9 gm. was reached. The patient again complained of nausea, chills and fever associated with the administration of the drug, so it was discontinued temporarily. A fourth course of the antibiotic was given in April and May 1958, 1.0 gm. intravenously. It was necessary to give 20 mg. of soluble hydrocortisone with the intravenous drip of amphotericin B. This controlled the nausea, vomiting and malaise quite effectively. Since May 1958 the patient's sputum has been consistently negative for blastomycetes, and he has remained in relatively good health, except for the symptoms produced by his extensive pulmonary scarring. Throughout the patient's many hospitalizations he has been followed by various members of the thoracic surgery division who have been consulted in regard to the possibility of pulmonary collapse therapy. It has been their feeling that no surgical procedure could be risked in view of the patient's reduced pulmonary vital capacity.

This patient has consistently had a negative blastomycin skin test throughout the entire course of his disease. Prior to amphotericin B therapy his complement fixing antibody titers were positive at a titer of 1:64. He continued to have a positive complement fixation test titer of 1:32 when last checked in May 1959.

Case v. H. G. is a fifty-six year old white, male farmer from Kentucky who had progressive onset of weakness and malaise in 1949, apparently associated with a prolonged episode of chills and fever at that time. In 1951 a verrucous granuloma of the left upper lip developed which was identified as blastomycotic in origin. The patient was originally treated at the V. A. Hospital in Louisville, Kentucky, with stilbamidine, x-ray and potassium iodide. Trigeminal nerve involvement developed as a result of the stilbamidine therapy. Improvement followed the first course of stilbamidine therapy; however, the disease recurred within six months, and he was retreated with the same drug. He was first seen at the V. A. Hospital in Ann Arbor, Michigan, in July 1956, at which time he was given 9.6 gm. of 2-hydroxystilbamidine in a daily dosage of 450 mg. per day. Improvement was noted, but exacerbation again occurred, and the patient was readmitted to the hospital in March 1957, for a course of amphotericin B therapy. He had had a total dosage of 46.0 gm. of the aromatic diamidines. At that time, extensive cutaneous granulomas were present over the nose, the entire right side of the face, and the left eyelid. Roentgenograms of the chest showed bilateral hilar calcification, as well as small peripheral calcifications in the upper left lung. There was no evidence of active pulmonary disease. The hemoglobin was 11.5 gm. per cent, hematocrit 60 per cent, white blood count 11,000 per cu. mm. with a normal differential count. The urine was normal. Stool guaiac examination was negative. The initial liver function tests were normal, and remained so during the amphotericin B therapy except for the cephalin flocculation test, which increased from normal to 3-plus at forty-eight hours. The blood urea nitrogen consistently was found to be below 15 mg. per cent. The patient was treated daily with 50 mg. of amphotericin B per day suspended in 1,000 cc. of 5 per cent glucose in water. He experienced nausea and vomiting and generalized constitutional reaction to this therapy. He also received 20 mg. of prednisolone and 50 mg. of chlorpromazine prior to each amphotericin B injection. Following the course of therapy the nausea and vomiting continued for several weeks, and it was not until he was given an ulcer regimen that improvement in these symptoms was noted. There was no radiologic evidence of gastric or duodenal ulcer. Since the patient's discharge from the Ann Arbor V. A. Hospital on May 11, 1957, he has remained completely free of all evidence of active disease. He was last checked in July 1959. This patient's blastomycin skin test and complement fixing fixation test have both been consistently negative throughout the entire course of his illness.

Case vi. W. J. is a sixty-nine year old white male carpenter from Muskegon, Michigan, who was admitted to the University Hospital in Ann Arbor, Michigan, in April 1957. The patient stated that some five months previously he had what was diagnosed as severe influenza. This subsided on symptomatic therapy; however, some three months prior to his

admission, he noted a progressively enlarging granuloma of the tip of the nose. His referring dermatologist had correctly identified this cutaneous lesion as North American blastomycosis. No other physical abnormalities were noted on careful examination. The patient had had no other serious illnesses. Physical examination was essentially normal except for the exophytic, verrucous granuloma over the entire end of the nose. A roentgenogram of the chest was reported as showing no evidence of present or past pulmonary disease. The patient had had no previous therapy directed toward his North American blastomycosis. He was treated with intravenous injection of 50 mg. doses of amphotericin B, suspended in 1,000 cc. of 5 per cent glucose in water. These were given by slow intravenous drip over a period of approximately six to eight hours. There were no untoward effects other than mild nausea during the twenty consecutive days that the drug was administered. The blood urea nitrogen remained below 14 mg. per cent at all times. Hematopoietic and hepatic studies were consistently normal. The patient was discharged one month from the date of admission with complete regression of the cutaneous lesion. In the twenty-six months since discharge from the hospital there has been no sign of further activity. This patient's blastomycin skin test was and has been consistently negative. His complement fixation test, initially positive in a titer of 1:4, became negative three months following amphotericin B therapy, and has remained negative to date.



FIG. 4. Case VII. Characteristic granuloma of the skin.

CASE VII. E. M. is a forty-one year old white male laborer who was admitted to the University Hospital in December 1957, because of a verrucous, granulomatous cutaneous lesion across the glabella, extending to the cheeks and upper and lower eyelids. (Fig. 4.) The patient stated that while at work as a laborer for the State of Michigan Highway Department, he sustained a blow across the bridge of the nose in May 1957. In the area of the trauma, he alleged, multiple nodules appeared which developed into the extensive cutaneous lesion present at the time of his admission to the hospital. It was considered significant that in March 1957, some two months prior to the development of the cutaneous lesion, this patient had had an episode of pain in the upper left side of his chest, cough and low-grade fever. Roentgenograms of the chest taken at that time showed a hazy parenchymal infiltration involving the left apex and extending down into the medial portion of the left first anterior interspace and into the upper pole of the left hilum. When the patient was admitted to the University of Michigan Medical Center in December 1957, a roentgenogram of his chest was reported as being completely normal, and gave no indication whatsoever of previous or present disease, except for the raised, verrucous, granulomatous lesion of the face. B. dermatitidis was demonstrated with ease from pus expressed from the cutaneous lesion. Gastric analysis was negative for the blastomycetes on direct examination and culture. Amphotericin B was given to this patient in a daily dosage of 50 mg. in 500 cc. of 5 per cent glucose in water. The patient was allowed to regulate the rate of the intravenous drip, and toward the end of the twenty-one days which were required to complete the total dose of 1.0 gm. he had increased the rate of the intravenous drip to the point that a bare three hours were required to receive the 50 mg. dose. This patient complained of no untoward symptoms during or after the administration of amphotericin B. All laboratory studies, including checks on the renal status, were entirely normal. The patient was discharged from The University Hospital on January 6, 1958. He has been examined at regular intervals since the time of his discharge, and is completely free of any evidence of active North American blastomycosis. His blastomycin skin test and complement fixation test have been consistently negative.

CASE VIII. M. A. is a thirty-three year old white physician of Turkish ancestry from Toledo, Ohio. During the winter of 1957–1958 he had had repeated and prolonged infections of the upper respiratory tract. In January 1958, weakness, chills, fever and weight loss were first noted. Diagnostic studies performed at a Toledo, Ohio hospital revealed an abnormal density in the anterior segment of the upper lobe of the left lung. A presumptive diagnosis of neoplasm was made, and the patient had a left upper lobe lobectomy in June 1958. Culture of the pathologic specimen was positive for B. dermatitidis, and microscopic examination of the removed portion of the lung revealed a granulomatous lesion in which typical single budding structures could be seen. Two weeks postoperatively the patient was transferred to the University of Michigan Medical Center, Ann Arbor, Michigan, for consideration of amphotericin B therapy. No further sign of activity of this fungus disease

was demonstrable on careful physical examination. Nevertheless it was decided that a prophylactic course of 1.0 gm. of amphotericin B should be administered. This decision was based primarily upon the microscopic finding of typical blastomycetes in sections of the hilar lymph nodes that were removed at the time of operation. We interpreted this as evidence that the disease process had not been completely eradicated by the surgery which had been performed. Prior to amphotericin B therapy this patient had completely normal laboratory studies. He was given amphotericin B in a dosage of 50 mg. per day in 500 cc. of 5 per cent glucose in water. He tolerated the administration of this antibiotic poorly, and towards the end of the course of therapy it was necessary to allow him three to four days rest between each intravenous treatment. After five days of therapy the blood urea nitrogen rose to a level of 20 mg. per cent from a previous level of 15 mg. per cent. Large numbers of cellular casts as well as coarse and fine granular casts, white blood cells and red blood cells appeared in the urine, but disappeared after several days rest. Phlebitis also developed in the areas of the injection. A febrile response to 101°F. developed on two occasions during the administration of amphotericin B. Nausea, vomiting, emesis and anorexia also occurred throughout the entire course of the antibiotic. In spite of these toxic effects it was possible to complete the course of 1.0 gm. of the drug, and the patient was discharged from the University Hospital on August 2, 1958. There has been no evidence of recurrent disease. This patient's blastomycin skin test and complement fixation test have been consistently negative on all occasions.

COMMENTS

The first five of the eight cases of systemic North American blastomycosis reported are thought to represent the most severe form of the disease. These five patients had negative blastomycin skin tests, and four of the five had positive complement fixation tests. Furthermore, all five had had more than adequate amounts of aromatic diamidines without effecting cure. That any of these five patients reponded to amphotericin B is testimony for the potent antifungal effect of this antibiotic. Three patients (Cases I, III and IV) have given evidence of recurrence of their mycotic disease following amphotericin B therapy at the dose schedule used. One patient (Case I) has since had an apparent cure of the disease after receiving an adequate amount of the drug. Two patients (Case III and IV) have required retreatment on several occasions in order to control their disease, and it is doubtful that either of these two patients are or ever will be completely cured of their extensive disease, even though they have remained free of signs of activity for more than a year. Cases VI, VII and VIII are thought to represent the more common form of North American blastomycosis. None of these last three patients had had previous aromatic diamidine therapy. Their response to amphotericin B therapy was excellent, and it seems relatively safe to assume that these three patients represent cures. One patient (Case VIII) is difficult to evaluate. He had no cutaneous lesions and no demonstrable pulmonary lesions when therapy was administered. Nevertheless, in view of the finding of B. dermatitidis in the hilar lymph nodes at the time of operation, it seems likely that the potentiality of systemic disease did exist when therapy was initiated.

Some toxic effect of amphotericin B was evidenced by all patients except one patient (Case VII) who withstood the untoward effects of the drug remarkably well. The toxicity of amphotericin B can be minimized by administering the antibiotic every second or third day. The most serious evidence of toxicity encountered was azotemia and urinary casts (Case VIII). This subsided upon withdrawal of the drug for a few days, and it was possible to resume and complete the therapy. This has been the experience of others using this drug. This problem has become increasingly serious, and in several instances azotemia has forced us to make the intervals between therapy so long that it has been impossible to administer adequate amounts of amphotericin B. The other, less significant toxic effects of the drug, nausea, vomiting, anorexia and fever, seem to be quite well controlled by the concomitant use of the corticosteroids administered either orally or intravenously. We realize that there may be serious question as to the wisdom of administering steroid hormones to persons with systemic granulomatous disease; however, we have not as yet encountered any evidence of undesirable effect. The use of the steroid hormones was necessary in several of the patients in this report in order to complete the amphotericin B therapy.

The dosage required to effect apparent cure in North American blastomycosis still remains to be determined. It does appear that a smaller total dosage of amphotericin B is required in this fungus disease than in cryptococcosis, histoplasmosis and coccidioidomycosis. A total dose of 1.0 gm. has effected apparent cure in five of the reported eight patients of our series, and a dose

of 1.5 gm. was effective in a sixth patient. As previously mentioned, the two remaining patients of our series of eight have extensive chronic, systemic disease of a nature which does not seem curable by any form of chemotherapy.

Unfortunately, we have not been in a position to perform blood serum levels of amphotericin B during the administration of the drug. Adequate blood levels can be maintained for at least forty-eight hours following a single intravenous administration of amphotericin B. In view of this finding it seems advisable to administer the drug at intervals of every other day rather than consecutively, to minimize the unpleasant effects.

We have not noticed any clinical evidence of induced resistance to amphotericin B even though as many as four separate courses were administered to one of our patients. Increased resistance has been demonstrated in several species of candida [*115,116*]. The clinical therapeutic effect was apparently just as great during the administration of the fourth course of amphotericin B as during the first course of therapy.

SUMMARY

There is increasing evidence of occurrence of a subclinical pulmonary form of North American blastomycosis, resembling the benign pulmonary form of coccidioidomycosis and histoplasmosis, which may be more prevalent than is generally thought. It is probable that North American blastomycosis is acquired by inhalation of the organism and that all patients with the disease so acquired have the potential for systemic spread. The only true cutaneous form of the disease is that rare type which is acquired by primary inoculation of the B. dermatitidis through the skin. Such an instance is recorded.

The results of intravenous amphotericin B therapy in eight patients with systemic North American blastomycosis are recorded. The first four of these patients were previously reported, and this report constitutes a follow-up. Five of the eight patients had proved resistant to massive aromatic diamidine therapy. All eight patients responded to amphotericin B therapy. Three of the patients have had recurrences following amphotericin B therapy, although they have been clinically free of recurrence for over one year at the time of this writing. Five of the eight patients received a total dose of 1 gm. of amphotericin B, one patient received 1.5 gm. of the antibiotic, one each received 4.0 and 4.5 gm. This amount is less than is used with the other deep mycoses.

Seven of the eight patients exhibited some evidence of toxicity during the administration of amphotericin B. Azotemia is the most serious of the toxic effects encountered during the administration of this drug. Fever, nausea, emesis and malaise, which accompany the administration of amphotericin B, can be reduced by the concomitant administration of judicious amounts of the corticosteroids. It also seems advisable to administer amphotericin B every other day in order to lessen the untoward toxic effect.

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Combined Staff Clinic

Tranquilizing Drugs

These are stenotyped reports of Combined Staff Clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Richard J. Cross.

Dr. Quentin Deming: In five short years, since the term *tranquilizer* was coined and since publication of the first clinical reports on the use of these agents in psychiatric institutions, the term itself and the suggestive trade names of the drugs have become part of our language. The drugs have had a major impact on institutional psychiatry and on clinical medicine (as well as on the financial status of the pharmaceutical companies involved). In addition, they have contributed to a renewed exploration of neurophysiology and neuropharmacology which may, in the long run, prove to be their most important contribution.

It is inevitable that a great deal of confusion should exist in a field expanding so fantastically fast. Such rapid growth could not have occurred without a tremendous advertising campaign directed at physicians, and this campaign has not helped to dispel the confusion. An ever-increasing number of drugs is being promoted; there are now about a score on the market. One drug company has even introduced essentially the same product under two names, recommending one for hypertension and the other for anxiety.

The drugs in question represent at least four different chemical classes, but they are all referred to as tranquilizers, or by semisynonyms such as *ataraxics*, mood normalizers, central relaxants, none of which has very clear meaning. They are recommended for the treatment of everything from psychosis to headache, from hypertension to bedwetting, and most of all for *anxiety*. All this has happened before there is any clear knowledge of the mechanisms or even the sites of action of the various agents.

It would be appropriate at this point to define a "tranquilizer" (it is a frightening term) but I must confess that I cannot. Dr. Berger, whose chemical classification I shall describe shortly and who is the pharmacologist responsible for the introduction of Miltown,® uses *tranquilizer* and *ataraxic* as interchangeable terms meaning "agents that quiet seriously disturbed psychotics, cause remission of schizophrenic and paranoic symptoms, bring peace of mind to overwrought neurotics, or antagonize the manifestations of hallucinogenic agents." This definition seems a little more expansive than the original purpose of the word and incorporates what he now believes can be accomplished with these drugs. It creates therapeutic success by definition.

Bello, writing in *Fortune* magazine, has given a simpler if somewhat inelegantly phrased definition, "The tranquilizers are compounds that reduce anxiety, agitation or emotional turmoil without putting a person to sleep." Another aspect which has been stressed by some observers is the ability of these agents to make patients cooperative, to induce an increase in suggestibility, and to produce placidity or docility.

It must immediately be apparent that it is impossible to make a completely clear distinction between these actions and sedation. The action of any drug is dependent on the dose. Phenobarbital, or any other sedative given in appropriate dosage, does reduce anxiety and has a calming effect, and does reduce muscle tension. Similarly, all the tranquilizers are sedatives, and in sufficient dosage have been observed to induce sleep and even to cause stupor or coma. It does not follow that these drugs are just new sedatives. Some of the agents which are called tranquilizers are obviously different from barbiturates, appear to have their predominant effects in a different area of the central nervous system, and appear to modify personality differently. Others are less easily distinguished from conventional sedatives.

It is likely that many familiar drugs would

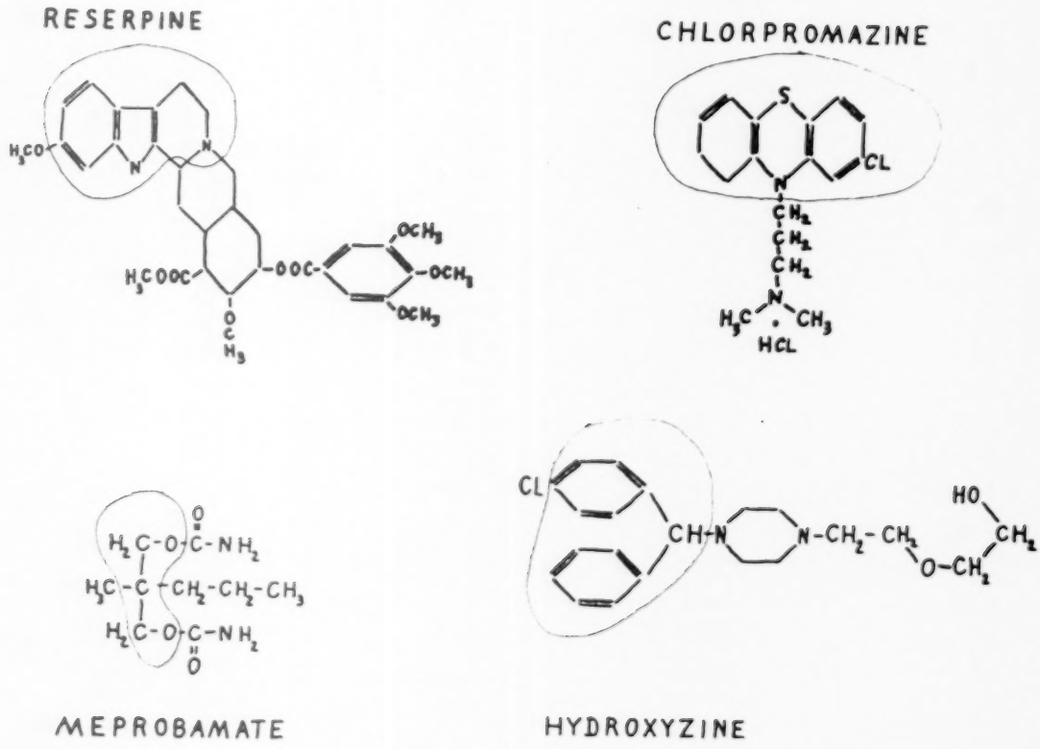


FIG 1.

have been classified as tranquilizers had the term been popular when they were introduced. (There is no more reason to group meprobamate with reserpine and chlorpromazine than there is to classify phenobarbital with them.) Conversely, if the term were not yet current, each of the "tranquilizing drugs" might be classified on the basis of some other action. Each has a variety of pharmacologic effects, some of which have nothing to do with tranquility. When such effects are being sought, tranquilization may be labelled toxicity; when tranquilization is being sought, these other effects may be labelled toxicity.

Figure 1 shows the formulas of representatives of four different classes of drugs which are referred to as tranquilizers. Let us first consider reserpine. The circle outlines the structure of serotonin. Because this structure can be identified in the molecule, Wooley and Shaw have related reserpine to several other groups of drugs with structural formulas in which serotonin also can be identified, namely lysergic acid diethylamide (L.S.D.) and the ergot alkaloids.

Brodie has pointed out that one could come quite close to the structure of norepinephrine if one drew this circle around the first two rings and broke the bond between the nitrogen and the first benzene ring. The possible significance of these two observations will be mentioned shortly.

In each of the other structural formulas the circle outlines the part of the molecule which (in the classification of Berger) is characteristic of a whole group of related compounds. Chlorpromazine is shown as a representative of the phenothiazines, meprobamate of the substituted propanediols, hydroxyzine as a representative of the diphenylmethanes.

In Table 1 are listed some members of each of these four classes together with the trade name of each. Note particularly among the phenothiazines related to chlorpromazine, the compound Phenergan.® We are familiar with this as an antihistaminic. We are also familiar with the fact that it has sedative properties. Perhaps it could be classified as a tranquilizer. Similarly, chlorpromazine and others in the group show antihistaminic and hypnotic properties. They also show the antiemetic properties which will be discussed subsequently.

Reserpine and the phenothiazines, while chemically different and probably different in their mechanism of action, are quite similar in their over-all effects on behavior. They are the

TABLE 1

Phenothiazines		Rauwolfia		Diphenylmethane		Substituted Propanediols	
Drug	*Trade Name*	*Drug*	*Trade Name*	*Drug*	*Trade Name*	*Drug*	*Trade Name*
Chlorpromazine	Thorazine	Reserpine	Serpasil®	Azacyclonal	Frenquel	Meprobamate	Equanil
Promazine	Sparine	Deserpidine	Harmonyl®	Benactyzine	Suavitil		Miltown
Mepazine	Pacatal	Rescinnamine	Moderil®	Hydroxyzine	Atarax	Mephenesin	Tolserol®
Prochlorperazine	Compazine			Phenyltol-oxamine	PRN		
Perphenazine	Trilafon			Adiphenine	Trasentine		
Trifluprom azine	Vesprin®			Meclizine	Bonamine		
Piperidinochlor-phenothiazine	NP208						
Promethazine	Phenergan						
Thiopropazate	Dartal®						

most potent tranquilizers and the agents which have shown particularly striking effects on psychotics. Their difference from conventional sedatives is convincing. They all modify autonomic functions.

Among the diphenylmethanes are four drugs marketed as tranquilizers and also two drugs familiar for other properties, the "antispasmodic" Trasentine® and the "antiemetic" bonamine.

The substituted propanediols were first studied as muscle relaxants. They are presumed to block "interneurons" because they appear to interfere with reflexes involving many synapses more than they interfere with the function of simple reflex arcs, at least at low dosage. Some consider meprobamate (which is Miltown and Equanil®) essentially a long-acting, orally effective mephenesin. Some believe its central action to be a reflection of its peripheral action; others believe its peripheral action to be a reflection of its central action. Its popularity, despite its comparative lack of potency, is related to its not surprising comparative lack of toxicity. It undeniably does affect the way people feel but it is quite misleading to have the common label of "tranquilizer" applied both to meprobamate and to reserpine and the phenothiazines.

If we understood how these drugs produce their effects the questions of nomenclature and therapeutic choice would be simpler. We do not. However, in a recent talk Dr. Bernard B. Brodie of the National Heart Institute discussed the pharmacology of these compounds and offered some theories about their actions. He attempted to relate the action of these drugs to their possible interference with normal chemical transmitters of nerve impulses in the brain. He discussed W. R. Hess's Nobel Prize–winning concept of two antagonistic, integrated systems in the mid-brain, the "ergotropic" and "trophotropic." He suggested that norepinephrine was the neurohumoral agent for the ergotropic system and serotonin that for the trophotropic system, and that monoamine oxidase was the enzyme responsible for the deactivation of both of them.

You will recall that Wooley pointed out a structural resemblance between reserpine and serotonin, and suggested that reserpine might act as an antimetabolite of serotonin. Brodie has pointed out a structural resemblance between reserpine and norepinephrine. Reserpine has been proved by the group at the National Heart Institute to deplete the brain and other tissues of both serotonin and norepinephrine. Brodie postulated that by blocking the binding of serotonin and leaving free a low but persistent concentration of newly synthesized serotonin, reserpine might stimulate the "trophotropic" system and invoke its central parasympathetic-like effects. Some of the drug's peripheral effects he accounted for by its depletion of norepinephrine from nerve endings. Chlorpromazine, he suggested, acted by blocking norepinephrine centrally.

This theory accounts for the similarities of the effects of reserpine and chlorpromazine (one stimulating the trophotropic system, the other blocking the ergotropic system), and for their distinctions. Their interactions with L.S.D., for instance, differ, as do some of their peripheral actions; reserpine is said to act on both chemical mediators peripherally. Finally, the action of Marsilid,® an inhibitor of monoamine oxidase,

TABLE II
CONDITIONS FOR WHICH TRANQUILIZERS HAVE BEEN RECOMMENDED

Major psychoses		Hypertension
		Tachycardia
Anxiety states (pathological)		
Anxiety (normal)		
Alcoholism (delirium tremens and withdrawal)		Nausea
Tension headache	←?→	Vomiting
Premenstrual tension		Vertigo
Tension		Refrigeration anesthesia
Colitis		
Asthma		Muscle tension
Pediatric	←?→	Athetosis
Petit mal	←?→	Dystonia
Bedwetting		Acute back strain
Making disturbed children cooperative		Cervical myositis
Alleviating homesickness	←?→	"Fibrositis"
Geriatrics		
Senile psychoses		
Confusion		
Quarrelsomeness		
Negativism		
Surgery		
Pre- and postoperative anxiety		
Potentiation of anesthesia		
Excessive interest in sex (human and canine)		

would be accounted for in the same system by its production of a delay in the removal of either neurohumoral agent.

To return to the clinical field, Table II presents a list of some of the conditions for which one or more of these compounds have been recommended. This list has been arranged in two categories. On the left are conditions in which the usefulness of the agents, if any, is presumably dependent on their action as tranquilizers. On the right are conditions in which their usefulness would appear to be related to a specific pharmacologic action other than tranquilization. It is uncertain which of the columns some of the conditions belong in, and these have been indicated by a double arrow and question mark.

Some of these uses appear to represent significant therapeutic contributions. The use of the agents in psychoses, anxiety, and nausea and vomiting will be discussed in some detail. I would emphasize also their use in hypertension, in control of the irascible senile patient, and perhaps in petit mal and in spastic conditions. Some of the conditions, I personally believe, are distressing even to find on the list. Perhaps the control of homesickness is the most startling.

There is another action of the phenothiazines and reserpine, not obviously shared by meprobamate, which must be remembered. It is their ability to potentiate the action of a variety of other drugs. At times this may be useful. It has been consciously employed in anesthesia. It may partially account for the usefulness of reserpine in combination with other antihypertensive agents. On the other hand, potentiation of drug action is a potential hazard for any patient receiving these agents. Barbiturates, alcohol and opiates may all produce more than the expected response in their presence.

All the drugs mentioned are capable of producing sensitization. With the phenothiazines, jaundice and photosensitization have been perhaps the most striking manifestations. With meprobamate, papular dermatitis has been noted particularly. Blood dyscrasias have been reported with several.

When a drug is used *because* it is a tranquilizer, its other pharmacologic actions are often described as side effects, desirable or undesirable as the case may be. The more potent tranquilizers produce more potent side effects. Both the phenothiazines and reserpine produce changes in various autonomic functions which are often disadvantageous. Both occasionally induce parkinsonism.

However, the most common adverse effects are precisely the result of tranquilization or, let us say, depression, enervation, and placidification. For example, reserpine is a useful antihypertensive agent. It is frequently stated that low doses are maximally effective. This is not literally true. A larger dose not only will frequently lower the blood pressure further but also may make a breadwinner unconcerned about the winning of bread. Loss of drive may make a debilitated patient stop making the effort to eat and drink. Even at conventional low doses, depression, or just an insufficient amount of anxiety, may make the drug undesirable. When the drug is used as a tranquilizer the same effect may be considered therapeutic, but the problem of deciding whether the modification of personality constitutes an improvement or a mistake may take the physician into a philosophical or sociological realm in which he may not feel completely competent.

We will now turn to a consideration of one of the specific pharmacological actions of some of these drugs which appears to be clinically useful. Dr. William Amols will discuss the management of nausea, vomiting and vertigo.

Dr. William Amols: The phenothiazine compounds have found their greatest clinical application in the modification of abnormal behavior states and in the treatment of emotional tension and anxiety, but they have other uses. For example, Phenergan (a phenothiazine derivative) was one of the early antihistaminics. Diparcol and Parsidol® were (and still are) used in the treatment of Parkinson's disease, which is quite interesting in view of the fact that one of the more prominent of the troublesome side effects of many of these compounds is the appearance of a syndrome resembling Parkinson's disease. Other clinical applications include their use in the induction of hypothermia, the potentiation of other drugs, antipruritus and antiemesis. It is in their antiemetic action that I have been principally interested for the past several years.

Until the advent of chlorpromazine the clinical management of vomiting was, in general, an unsatisfactory affair. Drugs which were effective in minimizing the nausea and vomiting of motion sickness were usually quite ineffective in controlling these symptoms when they appeared from other causes. Other less specific methods of treatment gave inconsistent and unpredictable results. The need for an effective antiemetic was clear enough but a useful means by which one could be developed was lacking. It was not until some of the neural mechanisms involved in the vomiting phenomenon were worked out by Dr. S. C. Wang and his coworkers that such a useful means became available. Wang et al. pointed out that basically there are two general types of emesis—one which is mediated reflexly over the vagal and sympathetic afferent nerves from the intestine, and one which results from the presence in the blood stream of certain circulating emetic agents such as apomorphine, morphine, Demerol,® ergot derivatives, digitalis glycosides, nitrogen mustards, and various abnormal metabolites such as occur in infections, intoxications, uremia and possibly radiation. In addition, there are the nausea and vomiting that result from psychological factors, from sights and smells, and from motion sickness.

A specialized group of cells situated in the highly vascular area postrema was discovered and named the Chemoceptive Emetic Trigger Zone (CETZ). Ablation studies have shown this to be the site upon which the circulating emetic agents seem to exert their principal effect, stimulating this region to activate the more deeply placed vomiting center which then brings about the complex, coordinated act of vomiting. Without this CETZ, the vomiting center remains completely resistant to circulating emetic agents. Stimuli arising within the intestine find their way directly to the vomiting center via the vagal and sympathetic afferents, and result in emesis without the intervention of the CETZ, which is completely by-passed. Vomiting of psychological origin likewise is believed to be mediated directly via the vomiting center without benefit of the Trigger Zone. The emesis resulting from motion sickness seems in some way to involve the Trigger Zone, although in just what way is not yet clear.

Chlorpromazine was found in dogs to block quite effectively the vomiting caused by circulating emetic agents, but to be ineffective against gastric irritants, particularly in small doses. In large doses, however, it blocked emesis from either source. In a general way this holds true when chlorpromazine is used in human subjects. It appears to be most effective in controlling the vomiting associated with infections, intoxications, neoplasms, radiation sickness and drug reactions. It is least effective in the vomiting due to gastric irritation and intestinal obstruction. With very large doses, often large enough to produce unpleasant side effects, even this type of vomiting can sometimes be eliminated. This suggests that chlorpromazine may depress the vomiting center in addition to blocking the CETZ.

This understanding of the neural mechanism of emesis has made possible a sensible and convenient method of screening antiemetic agents in animals by rating them against standard doses of chlorpromazine in their ability to block the vomiting which results from usually effective doses of centrally active emetics. In this way prochlorperazine was found to be three or four times as potent as chlorpromazine in dogs, and in human studies about two or three times as potent, dose for dose. Another phenothiazine (perphenazine) had a relative potency twenty-four times that of chlorpromazine, and in man was found to be in the range of five to eight times as effective.

Although earlier compounds such as Dramamine,® bonamine and Marezine® exhibit some degree of antiemesis in motion sickness, they do not compare with the phenothiazines in the control of vomiting of central origin. On the other hand, the phenothiazines seem to be relatively useless against motion sickness. Since the latter is believed to involve the CETZ, the reason for this is not clear.

Just why the phenothiazines should block emesis at the CETZ is not understood, but several theories have been devised in an effort to explain it. Perhaps the most attractive hypothesis is that based on the concept of competitive inhibition. When the phenothiazine compounds are placed directly on the CETZ they may actually produce emesis, but the amounts required for this are far greater than those for apomorphine and other centrally active emetic drugs. They are therefore very weak emetics. The theory of competitive inhibition holds that these compounds have a greater affinity for the receptor cells of the CETZ than have the usual emetic agents, and therefore block the receptors to these agents. Being such weak emetics they fail to stimulate the CETZ, and thus the vomiting center is not activated.

Another interesting and promising use for this group of compounds has recently come to light in a study being conducted at this hospital by Dr. Edmund P. Fowler, Jr., Dr. Robert M. Hui and myself. About two years ago it was discovered quite by chance that a patient who was very ill with violent vertigo, retching and nystagmus (which for want of a clearer understanding we called acute labyrinthitis) responded rather dramatically to the intravenous administration of a small amount of perphenazine, to the extent that not only did the retching stop but also the vertigo, her most distressing symptom, disappeared, and the nystagmus became hardly noticeable. When the effect of the drug wore off the symptoms returned, and this time were relieved by an intramuscular injection of 5 mg. of perphenazine. When, after a time, the symptoms again returned, oral perphenazine made her symptom-free for as long as she took this drug regularly. After about ten days the condition seemed to disappear.

This favorable effect on vertigo prompted an investigation into the usefulness of perphenazine in Meniere's syndrome. This clinical study is still under way, but some preliminary observations can be cited. Twenty-two patients with Meniere's syndrome have received treatment with perphenazine. Of these, fifteen have had sufficient follow-up to permit reporting on them at this time. All had vertigo as a prominent feature of the syndrome. All were having their attacks with sufficient frequency and regularity, and for a long enough time prior to the starting of treatment, that any major change in their pattern would not be likely to occur on the basis of chance alone. Seven of the fifteen patients had no further attacks after starting treatment. Of particular interest is the fact that the remaining eight patients receiving the drug continued to have their attacks with more or less the same frequency, at least for a while, but in each instance vertigo was no longer a feature nor did they complain of nausea, retching or vomiting. Their attacks simply consisted of increasing tinnitus and deafness, and a "blocked" sensation in the affected ear. These results appear to indicate that while the entire symptom complex of Meniere's syndrome is by no means eliminated, the most troublesome component, that of vertigo with nausea and vomiting, is quite effectively suppressed by this drug. A larger series of patients will have to be studied for a longer period of time before any firm conclusions can be drawn, but these early observations seem most promising.

DR. DEMING: We have thus far been on firm ground: the use of a drug to accomplish a specific change in function. The goal is definite, and methods for evaluating the effectiveness of therapy are comparatively simple. Now we will move to a mistier realm. Dr. Hamilton Southworth has undertaken the very difficult job of estimating how useful the tranquilizing drugs may be to the internist in office practice.

DR. HAMILTON SOUTHWORTH: It has been estimated that in 1958 over fifty million prescriptions for tranquilizers were filled. A portion of this vast amount was used in the care of institutionalized psychiatric patients, but the great majority must have been prescribed by internists and general practitioners who have been sold (or oversold) on their use. We should be accustomed by now to the overuse of new compounds that have been cleverly promoted, after watching what happened to multivitamins, cortisone and antihistamines. Tranquilizers are now in the boom phase, and realistic appraisal of their worth is still most difficult.

In general medicine, tranquilizers are used (1) to relieve tension and anxiety in actively

functioning people, (2) for psychoneurosis and diseases with a psychosomatic component such as peptic ulcer, ulcerative colitis, fibrositis and asthma, and (3) for certain special effects in hypertension, nausea and vomiting, vertigo, hiccoughs, and in disturbed senile patients.

It is most important to make the distinction between (1) and (2). Psychoneurotics are sick and to a greater or lesser extent cannot function adequately, and need therapy. However, perhaps an even greater use of tranquilizers has been to tide fairly normal people over periods of stress.

When I get up to speak, certain things often happen in my epigastrium and knees that are not altogether pleasant. It would be very nice to take a tranquilizer, but if I did, I certainly would not do my best. Anxiety and tension are important motivating forces in human progress, and any attempt to suppress them when they are not pathological but just physiological should be condemned.

The second category is a different proposition. Psychoneurotics who are disabled by their disease to a greater or lesser extent need treatment. Tranquilizers are of assistance, as a spate of articles published in the last four years attests. The problem is whether they help any more than other, older medications such as phenobarbital or chloral hydrate, or even placebos. It is here that the literature, viewed critically, is most disappointing. There are almost no accounts as yet of studies that were well conceived and that one can be sure were well controlled with double-blind technics and other safeguards to make them statistically significant. Reading over the best of what there is leaves one in real doubt whether that most popularized of the tranquilizers, meprobamate, has any advantage over the barbiturates in the therapy of psychoneurotics. Furthermore, the stronger phenothiazine derivatives (chlorpromazine, promazine, prochlorperazine or Compazine,® etc.) have enough inherent risk of such toxic effects as blood dyscrasia and, in the case of chlorpromazine of jaundice as well, to make their use somewhat questionable in the relatively mild psychoneuroses and psychosomatic diseases. The rauwolfia alkaloids are now used very little in internal medicine except in the therapy of hypertension. Other compounds listed by Dr. Deming and the newer drugs described by Dr. Amols have still not been studied adequately, except perhaps in some of the special situations listed in the third category for one to render any good judgment.

In the absence of any real backlog of sound published reports, I have tried to sample current opinion by asking about a dozen attending physicians on the staff of this hospital what use they make of tranquilizers in their practice. All but two of these physicians make house calls and serve as the personal physician for most of their patients.

The first question asked and the response obtained were:

1. For daytime sedation, during the last three to six months, have you used the following drugs, and in what relative proportions: meprobamate, phenobarbital, chloral hydrate, any others?

Phenobarbital: spread 25 to 95 per cent (average, 53 per cent)
Meprobamate: spread 0 to 60 per cent (average, 35 per cent)
Chloral hydrate: spread 0 to 20 per cent (average, 7 per cent)
Others (compazine and chlorpromazine mentioned): (average, 5 per cent)

This orients the problem in terms of daytime rather than night sedation and aims to compare the use of meprobamate with phenobarbital and chloral hydrate, and also with any other preferred tranquilizer. Perhaps the use of the word sedation was not optimal, but you will note first the tremendous spread in the relative use of these compounds by different physicians. Second, you will see that phenobarbital is still in a commanding lead. Third, it is obvious that the other tranquilizers are used very little by these practitioners.

2. Do you generally prefer meprobamate, phenobarbital or some other drug (please specify) for

Anxiety symptoms

Meprobamate preferred by 64 per cent of physicians
Phenobarbital preferred by 36 per cent of physicians
Others preferred by 0 per cent of physicians

Mild reactive depressions

Meprobamate preferred by 36 per cent of physicians
Dexamyl® preferred by 36 per cent of physicians

Chlorpromazine preferred by 19 per cent of physicians
Phenobarbital preferred by 9 per cent of physicians
Others preferred by 0 per cent of physicians

Patients who are just hyper-reactors

Phenobarbital preferred by 82 per cent of physicians
Meprobamate preferred by 18 per cent of physicians
Others preferred by 0 per cent of physicians

The second question aims to break down the preference for these compounds into specific disease patterns. Again there is a large difference of opinion, but meprobamate comes out surprisingly well in both anxiety symptoms and mild reactive depressions while phenobarbital is way ahead in the treatment of those who are just hyper-reactors, if any treatment is really required. Dexamyl, a combination of Dexedrine® and Amytal,® occupies an important place in the treatment of depression.

3. Which do you think has the greater incidence of unpleasant side effects, phenobarbital or meprobamate?

Meprobamate: 30 per cent of physicians
Phenobarbital: 30 per cent of physicians
No difference: 40 per cent of physicians

The third question aims to find out if the advertised lack of toxicity and side effects for meprobamate has been substantiated. You will see that phenobarbital and meprobamate came out exactly equal in this vote.

4. How do you think phenobarbital and meprobamate compare as to predictability of effect at standard doses?

Phenobarbital considered more predictable by 89 per cent
Meprobamate considered more predictable by 11 per cent

The fourth question raises the important problem of predictability of effect at standard doses, and you will see that phenobarbital is regarded by a great majority as superior in this regard.

5. What is your preferred drug in case of

Acute vertigo

Dramamine® preferred by 45 per cent of physicians
Chlorpromazine preferred by 33 per cent of physicians
Bonamine preferred by 11 per cent of physicians
Phenobarbital preferred by 11 per cent of physicians

Intractable vomiting

Chlorpromazine preferred by 90 per cent of physicians
Compazine preferred by 10 per cent of physicians

Intractable hiccoughs

Chlorpromazine preferred by 78 per cent of physicians
Phenobarbital preferred by 11 per cent of physicians
Dactil® preferred by 11 per cent of physicians

6. Give a very rough guess as to the percentage of your hypertensive patients with blood pressure over 180/110 mm. Hg now taking reserpine, barbiturates, other antihypertensive drugs.

Percentage of patients on reserpine: spread 10 to 70 per cent (average, 38 per cent)
Percentage of patients on barbiturates: spread 1 to 50 per cent (average, 21 per cent)
Percentage of patients on others: (average, 2 per cent)

7. In the disturbed senile patient do you employ the following drugs frequently or rarely?

Chloral hydrate: Used frequently by 90 per cent* of physicians
Chlorpromazine: Used frequently by 80 per cent of physicians
Meprobamate: Used frequently by 60 per cent of physicians
Phenobarbital: Used frequently by 30 per cent of physicians
Promazine (Sparine®): Used frequently by 20 per cent of physicians

The fifth, sixth and seventh questions are directed at the use of compounds in some of the specific problems listed previously in the third category. You will see that chlorpromazine has established its place in the treatment of intractable vomiting and hiccoughs, and is second only to Dramamine in vertigo. The newer compounds

* Thirty per cent specified that use was particularly for night sedation.

described by Dr. Amols were not yet adequately known when this sampling of physicians' opinions was made in November 1957.

The hypertension question can of course only be answered by a very rough estimate. Here again the spread in the answers (as in the case of reserpine, which some used in 10 per cent and some in 70 per cent of their hypertensive patients) is apparent. The question was purposely phrased to include patients with fairly mild hypertension, and it appears that in this over-all group a little more than half receive some medication and about twice as many are given reserpine as phenobarbital.

The last question, relating to the disturbed senile patient, does not specify between day and night sedation, and this is probably why chloral hydrate ranks so high. Phenobarbital is low because of its tendency to cause confusion in the aged. Chlorpromazine seems to rate slightly above meprobamate in this problem.

I must emphasize again that the physicians who filled out this questionnaire constitute a very small sample, and as attending physicians on the medical service of one teaching hospital are not at all representative of the country at large.

In summary, I should like to leave you with the realization that the place of the tranquilizers in internal medicine has not yet been clearly delineated. I am sure they have a place, but so far this seems to have been more securely established as a result of their special effects, such as against vomiting and hypertension, rather than as a result of their over-all tranquilizing action. There has been much overenthusiasm, and the conservative clinician is now cautiously trying out some of the compounds and contrasting them with his older methods of treatment. He is far behind the pharmacologist in the use of the newer compounds, but in the absence of definitive published clinical studies this is just where he should remain.

Dr. Deming: The place of tranquilizers in the practice of internal medicine is still uncertain, but their impact in psychiatry has been less equivocal. Dr. Sidney Malitz, Associate in the Department of Psychiatry, in charge of the Department of Experimental Psychiatry at the Psychiatric Institute, has undertaken a discussion of their usefulness in this field.

Dr. Sidney Malitz: The term "tranquilizer" has been severely criticized by many, and countless other substitutes such as "ataractic," phrenotropic agent," etc. have been suggested. In this discussion, by tranquilizer is meant a drug producing relief of tension and anxiety with diminution in motor hyperactivity without the profound drowsiness which barbiturates would induce in producing an equivalent effect. As will be emphasized later, this does not mean that drowsiness is not produced by some of these drugs.

Because the effects of these drugs are so different in hospitalized patients and those out of hospitals, I shall describe their indications and effectiveness under these two headings.

Hospitalized Patients. The most obvious and dramatic effects of the tranquilizing agents have been observed in hospitalized patients. Particularly benefited has been that group of hyperactive, assaultive, patients who have been severe therapeutic and management problems, frequently attacking hospital personnel and other patients, often ripping off their clothes and destroying property. In the past it was often necessary to keep them locked in a bare ward or in seclusion for much of the time. Diagnostically this group included a large number of catatonic schizophrenic excitements, agitated depressions, senile agitations and manic states of the manic-depressive psychosis. Most notably successful in the calming effect on these patients have been the phenothiazine and rauwolfia groups. The phenothiazines are the quickest acting and most effective. These drugs have also been used in the treatment of hyperactive mental defectives and in the withdrawal stages of hospitalized drug addicts. It is most impressive to tour the wards of a state hospital and to see now curtains, plants and other signs of domestic living where previously there had been nothing but bare walls for fear that the patients would destroy everything in sight. Those patients who in the past ran around naked and screaming are now neatly dressed, no longer incontinent, and either quietly idle or engaged in some form of occupational therapy. This experience has been universal in mental hospitals throughout the world. The dramatic improvement in these patients cannot be attributed, as some have claimed, solely to the "suggestion" effect of a new preparation which is frequently accompanied by great enthusiasm and increased energy on the part of the hospital staff. It is true that such a change in the staff's attitude often does bring about a transient improvement in the patient popula-

tion, but such effects are all too short-lived. The improvement with these drugs has lasted far longer than is seen with "placebo effect" agents.

The phenothiazine group has been most effective in controlling the excitement and hyperactivity of acute alcoholic hallucinosis and delirium tremens. The substituted propanediol group, the most prominent member of which is meprobamate (marketed as Equanil and Miltown), is of little or no value in the group of hospitalized patients just described. Frenquel® was originally recommended for the treatment of acute hallucinations, but its effectiveness has not been substantiated in subsequent studies. The severely deteriorated, withdrawn, vegetating, chronic hospital patient does not respond well to any of the tranquilizers or, unfortunately, to any other therapy we have available today.

Non-hospitalized Patients. These drugs are much less effective in outpatients than in the hospitalized group. There are two chief reasons for this difference. First, the symptoms which these drugs control best, namely, hyperactivity, unbearable anxiety and tension and assaultiveness, occur predominantly in hospitalized patients. If these symptoms play a prominent role in the clinical picture of the outpatient, hospitalization usually becomes necessary. Second, there is a tendency for outpatients not under the regulatory discipline of the hospital to discontinue these drugs as soon as unpleasant side effects develop. They will often stop the medication after a day or two, before beneficial effects of the drug have had a chance to appear. Some side effects, such as drowsiness and coordination difficulty, may cause impairment in a patient's work ability and in other daily functions such as driving a car and handling machinery. These problems are less important in a hospitalized population.

Tranquilizers have proved most effective in the severe anxiety neurotic who develops periodic attacks of panic, usually associated with such symptoms as hyperventilation, marked fears of impending death, pallor, tachycardia and extreme restlessness. The rapidly decompensating, ambulatory schizophrenic on the verge of a complete break may with these drugs avoid hospitalization. Drugs of the phenothiazine group, such as Thorazine,® Sparine, Trilafon® and Compazine, are most effective in these patients. The rauwolfia group is somewhat less effective because these drugs do not act quickly enough; they often require several days of administration before becoming effective.

Meprobamate has been of little value in this group. On the other hand, in patients with mild to moderate anxiety and tension, the meprobamate group is of some value, especially when one would not want to use the more potent rauwolfia and phenothiazine groups because of their unpleasant and sometimes serious side effects. There is some question, however, as to whether meprobamate is any more effective than phenobarbital in patients with mild anxiety. Obsessive-compulsive patients react poorly to all of the so-called tranquilizers and frequently become preoccupied and disturbed further by the side effects resulting from their usage. It is difficult to predict the reaction of patients with phobias although it is worth while to try the more potent tranquilizers. Some phobic patients who are afraid to travel to the doctor's office may improve sufficiently to make the trip and receive psychotherapy or other necessary treatment. Others, of course, may become phobic about taking the medication and get worse.

Most of us at one time or another have seen patients with marked paranoid ideation existing out of a hospital setting. Some of these patients decompensate further under appropriate internal or external stress and require hospitalization. The phenothiazines have sometimes proved effective in preventing hospitalization in some of these persons, although others have become suspicious about the medication and about the side effects, feeling that they are being influenced in some way, and will break off treatment. The phenothiazine and rauwolfia groups seem more effective than the meprobamate group for this type of patient.

Great care should be exercised in administering these drugs to depressed patients. Drugs of both the phenothiazine and rauwolfia groups have been reported to intensify already existing depression and sometimes to be associated with the development of a depression when it has not previously existed. This is especially true of the rauwolfia group. The treatment of choice for depression still is electric shock. Temporizing with a depressed patient may result in a suicidal attempt. Meprobamate in combination with benactizine has recently been recommended for the treatment of depression, but the effectiveness of this treatment has not yet been established.

Drugs of the diphenylmethane group have been uniformly disappointing in the treatment of

both hospitalized and non-hospitalized mental patients. Frenquel, while it has no side effects, does not have any appreciable clinical effects either. Atarax® has few side effects but is so mild in its action that it is of little value in moderately and severely anxious patients and of no value in ambulatory psychotics. Suavitil was originally recommended for obsessive patients but its value has not been substantiated.

In general, one can say that the results with all tranquilizers in outpatient neurotics and ambulatory psychotics are not nearly as promising as are the results with the hyperactive, highly agitated hospitalized group.

As previously mentioned, the administration of these drugs is often complicated by a variety of undesirable side effects. While the phenothizaines remain the best all-around tranquilizers, they are also associated with the greatest amount of side effects. Fortunately, few of these are considered serious. A cholangiolitic jaundice may develop which usually subsides when the drug is discontinued. A higher incidence of jaundice has been noted in patients with a previous history of gallbladder disease or biliary obstructive symptoms. Agranulocytosis may also occur, but it is extremely rare and is apparently due to individual sensitivity to the drug. Some of the less serious but frequently annoying side effects are drowsiness, fatigue, allergic skin reactions, hypotension, diarrhea or constipation, increased appetite, photosensitivity, nasal stuffiness, dizziness, lactation and edema of the hands and feet. A parkinsonian picture may develop which subsides when the drug is discontinued.

Of equal importance are the psychic side effects observed. Some patients develop marked feelings of depersonalization and unreality. Patients will frequently complain of being in a "dream state" and are frightened by feeling out of contact. This is a very common cause for spontaneously discontinuing the drug in outpatients. Others complain of vivid night dreams, and still others of decreased sexual potency. The latter may actually be a physiologic disturbance rather than a psychic one. Depression has already been mentioned. Occasionally, acute psychotic reactions with organic confusion symptoms may be precipitated by these drugs. Recently seizures have been reported upon the sudden withdrawal of Thorazine and Sparine in patients taking relatively high dosages. A number of these patients gave a previous history of brain damage but some did not.

The side effects of the rauwolfia group are the same as those of the phenothiazines except for a much higher incidence of depression. There have been no reports of jaundice. Depression may be so severe as to require hospitalization and electric shock therapy. There have been several reports of suicide after drugs of this group are given. Epileptiform seizures have been reported early in treatment but are not frequent. Gastrointestinal hemorrhages have also been known to occur, and this group of drugs should therefore be used only with great care in patients with gastrointestinal disorders.

The side effects of meprobamate are few. Drowsiness appears to be the chief side effect. There have been some reports of skin rash and non-thrombocytopenic purpura. There have also been infrequent reports of fever, fainting and angioneurotic edema. To date there have been no reports of fatal blood dyscrasias. Possible habituation has been reported. It is interesting to note that habituation does not appear to occur with the phenothiazine or rauwolfia groups. This may be because there is no true pleasure component associated with their intake since the side effects tend to balance off any elements of excessive gratification associated with the relief of troublesome mental symptoms. Since the side effects of meprobamate are either slight or absent, the patient has the opportunity to get more real pleasure from the intake of this drug. Withdrawal reactions and seizures have been reported following abrupt termination of this drug.

There is no rule as to the amount of drug necessary to produce tranquilizing effects. Because of the great individual variation in response it is necessary to evaluate each patient's response individually with the aim of attaining that dosage which will produce maximal clinical effects with minimal side effects. Dosages recommended by the manufacturers of these drugs may be used as a starting point, but it will frequently be found that much smaller doses suffice, or occasionally that much larger dosages may be necessary. Side effects also vary tremendously from patient to patient; some develop them at an exceedingly small dosage level, while in other patients very high dosage levels of the drug produce minimal side effects. For example, some patients receiving 150 mg. of Thorazine a day are so disturbed by drowsi-

ness, dry mouth and feelings of depersonalization that they are virtually unable to function. Others taking 1,000 mg. a day may achieve a satisfactory level of tranquilization with virtually no side effects. Some patients maintained on these drugs for a period of months may begin to slip because of a tolerance which appears to develop, especially with the phenothiazine and rauwolfia groups. This finding also is highly variable. Some investigators have recommended using the development of the parkinsonian syndrome as the end point in determining the optimal beneficial level of the drug. In our experience, this has not been helpful since many patients seem to derive benefit from the phenothiazines and rauwolfia drugs without developing any parkinsonian features. Initially, the literature cautioned against the use of barbiturates in conjunction with the phenothiazines, stressing the marked potentiation of the former by the latter. While it is true that potentiation frequently occurs, the degree of potentiation is highly variable and must be individually assessed.

Many patients relapse when these agents are discontinued, and it is necessary to carry some on maintenance dosages for several years. Many more studies are needed of long term effects of these drugs.

The use of the phenothiazines in conjunction with electric shock treatment is still a highly debatable issue. Several cases have been reported of circulatory collapse and death following the combined use of electric shock treatment and this group of drugs. Other investigators claim they have given hundreds of shock treatments in combination with Thorazine, Sparine and related drugs without sequelae. At present it would appear most expedient to discontinue the use of tranquilizing drugs before administering shock treatment.

The exact relationship between psychotherapy and the tranquilizers has yet to be worked out satisfactorily. Certain patients appear to be made more approachable by the use of these drugs. Whether or not the tranquilizing agents actually shorten psychotherapy has not yet been verified. The ideal tranquilizer will prove to be not a "magical pill" but a safe drug with a minimum of side effects capable of controlling adequately the disrupting influence of excessive fear, rage and anxiety so that a person can cope with life's problems in optimal fashion free from these major handicaps.

DR. FRANKLIN M. HANGER: I am sure that we are all well accustomed to coincidences in the realm of scientific discovery. But it does seem remarkable that four new groups of compounds differing from one another both chemically and pharmacologically, but having great similarities in their effect on behavior, should be discovered almost simultaneously. Is there any good reason why this should have happened?

DR. DEMING: I do not think it has happened. Of course the pace of drug development has accelerated tremendously in recent years and some coincidences are to be expected. However, rauwolfia is an old drug in India. It is a coincidence that it was introduced in the West only a short time after the phenothiazines were introduced in France—the first for hypertension, the second for hypothermia. These two classes do have similar effects on behavior, and when the catchy, descriptive term "tranquilizer" was coined, it spread to both. The other groups discussed do not really have comparable effects on behavior but have enough such effect to have led to their introduction under the same catchy label for sales reasons. We have seen not a scientific coincidence but a bandwagon use of promotional terminology combined with the development of a somewhat new approach to the use of drugs to affect the psyche.

DR. JOHN DEAN: I should like to ask Dr. Southworth if he thinks that reserpine affects the underlying course of uncomplicated hypertension, or does its use merely provide symptomatic relief from anxiety for the patient and perhaps even for the physician?

DR. SOUTHWORTH: To my knowledge there is no clinical study which as yet provides an answer to this question. Essential hypertension commonly remains in an uncomplicated stage for ten or more years, while rauwolfia alkaloids have been used extensively for only five years. Any answer therefore must be in terms of personal opinion. This will depend on whether one believes that in essential hypertension the elevated peripheral resistance causes or at least aggravates the arteriolar lesions. In the advancing cases it is quite possible that each aggravates the other and that reserpine may help to break a vicious circle. In the uncomplicated case, however, we still lack real evidence that the underlying course of the disease is modified.

STUDENT: It has been mentioned that the phenothiazines are of no value in the treatment of motion sickness. I wondered if attempts have

been made to combine them with antiemetics in the antihistamine group to see if a potentiating action could be observed?

DR. AMOLS: To the best of my knowledge this has not been done.

DR. FRED KATZ: I gather that the use of these drugs has greatly reduced the need for both facilities and personnel in our mental hospitals. I wonder if Dr. Malitz has any figures on the extent to which this has occurred?

DR. MALITZ, I can give you figures only for New York State. It may surprise you to know that contrary to the expectation that the need for facilities and personnel would be reduced, the advent of the tranquilizing drugs has resulted in an increased need for these facilities and personnel! The role of the attendant is no longer that of custodian. He now is actively engaged along with the psychiatrist and social worker in milieu therapy with previously inaccessible patients. There is now a crying need for additional doctors, nurses, social workers and attendants to aid in the rehabilitation of these patients. The advent of the open hospital which has been made possible, at least in part, by the use of tranquilizing agents also has required additional personnel.

Dr. Henry Brill, Assistant Commissioner of Mental Hygiene for the State of New York in charge of research and evaluation of these drugs in New York State, has reported that in the year 1955–1956 the state hospital population showed a decrease of some 500 patients in comparison with the increase of 2,500 the year before and the average rise of 2,000 per year for the previous decade. The same trend continued during 1956–1957, producing a further reduction of some 500 patients. It should be kept in mind, however, that the increased discharge rate has been attributed to a general stepping up of all forms of therapy, both new and old, of which the tranquilizing agents make up only one part.

Within the last two years, restraint and seclusion has been cut by 75 per cent. This is a mathematical expression of what has been a revolution in the care and treatment of hospitalized mental patients.

SUMMARY

DR. RICHARD J. CROSS: The tranquilizing agents are not one but several groups of compounds which differ from each other widely but have been classified together. Some of them have very useful properties unrelated to the common label of "tranquilizer." They all have undesirable side reactions, many of which result from their tranquilizing or other therapeutic properties. All of them do affect mood and alertness but not all in the same way or to the same degree.

Our understanding of the mechanism of action of these drugs is far from clear and will probably require a greater comprehension of normal neurophysiology. Conversely, the research scientists seeking such a greater comprehension have found these new agents to be useful tools, and this, in the long run, may prove to be their most important contribution. Studies of the relationship between the metabolism of these compounds and that of serotonin, norepinephrine and psychotomimetic agents such as LSD are yielding interesting results which may represent the beginning of an understanding of their pharmacology and an opening for a new approach in neurophysiology.

Chlorpromazine and related compounds have been found of great value in controlling vomiting, particularly when the Chemoceptive Emetic Trigger Zone is involved. Emesis due to motion sickness and gastric irritation is far more difficult to control. These compounds have shown a dramatic effect in suppressing the vertigo, nausea and vomiting of Meniere's syndrome.

In other medical conditions the tranquilizing drugs have proved to be of great value, although their effects are somewhat less clear-cut. As their name implies, their chief usefulness has been in relieving tension and anxiety in actively functioning individuals. However, unless due caution is observed, this active functioning may be impaired.

The management of hospitalized mental patients has undergone a major change since the introduction of these agents. Assaultive patients formerly handled only by restraint and isolation have now become amenable to treatment. The entire atmosphere of the mental institution has been altered. Outpatients are less amenable to such therapy, although in many these drugs have proved useful.

As is usually the case when potent new drugs are discovered, the introduction of the tranquilizing agents has been followed by a great wave of enthusiasm and considerable overuse of these compounds. As objective, well controlled clinical studies have become available, we have gradually increased our understanding of both the usefulness and the dangers of these

drugs. At the same time they are teaching us more about neuropharmacology which in due course will provide us with a clearer understanding of the mechanisms involved.

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Case Reports

"Lowe's Syndrome"*

Abnormalities in Renal Tubular Function in Combination with Other Congenital Defects

EDGAR J. SCHOEN, M.D., WITH THE TECHNICAL ASSISTANCE OF GEORGE YOUNG, A.B.
Oakland, California

INTEREST in the group of congenital metabolic defects in which aminoaciduria is present was kindled by Fanconi in 1936 [*1*]. Since that time many cases have been reported in which aminoaciduria, other renal defects, and rickets have existed in infants and children on a congenital basis. In 1952 Lowe and his co-workers [*2*] described three cases of a syndrome, apparently non-familial, consisting of aminoaciduria, organic aciduria, albuminuria, decreased renal ability to form ammonia, systemic acidosis, hydrophthalmos, retarded growth and development, hyporeflexia, decreased muscle tone and muscle mass, recurrent fever, high pitched cry, and rickets. The present report concerns double ovum twins in whom all but the last three of these findings were present. The discovery of these anomalies shortly after birth has offered a unique opportunity for early definition and treatment of some of the abnormalities involved, particularly those of the eye, and for the prevention of rickets.

CASE REPORTS

CASE 1. R. H., the older of double ovum male white twins, was born at Kaiser Foundation Hospital, Oakland, August 3, 1956, by breech delivery. He weighed 6 pounds, 2 ounces at birth. On discharge at age four days, his weight was 5 pounds, 8 ounces. His diet consisted of an evaporated milk formula and a vitamin preparation supplying 1,000 units of vitamin D daily. At the age of seventeen days the infant was brought to the clinic because of failure to gain weight. Bilateral corneal opacities, high palate, prominent epicanthal folds, tapered fingers and a small umbilical hernia were observed.

The mother had not been ill or exposed to radiation or toxins during pregnancy. Four older siblings, including double ovum female twins aged two years, were normal. There was no history of congenital anomalies or metabolic disease within the family.

At the age of two months the infant was admitted to the hospital for ophthalmic surgery. He was pale, thin and hypoactive. His weight was 8 pounds, 6 ounces; length, 21 inches; head circumference, 14¾ inches; chest circumference, 13½ inches. The anterior fontanelle measured 3 centimeters in length and 2 centimeters in width; the posterior fontanelle was closed; there was no craniotabes. The pupils failed to react to light. A dense, white, irregular cataract occupied the center of each lens; surrounding it was a small portion of clear lens. Ocular tension was 28 mm. in each eye. The pupils were pinpoint and did not dilate because of dense posterior synechiae. Slit lamp examination failed to reveal evidence of cystine crystals in the conjunctivas. In addition to the physical defects previously observed, muscle tone was flabby and there was generalized hyporeflexia and hyperextensibility of the extremities. The infant was not observed to smile, and apparently could not lift his head or chest from the prone position.

On admission the white blood cell count was 6,450/cu. mm. with a normal differential count; the blood hemoglobin level was 8.8 gm./100 ml.; the erythrocyte count was 4.8 million/cu. mm., the erythrocytes appearing small and pale on blood smear. Cystine crystals were not present in the bone marrow. Examination of the urine revealed a specific gravity of 1.022, pH greater than 8.0, response to the Sulkowitch test 2-plus, no albumin, sugar or acetone. From five to fifteen leukocytes per high power field, and an occasional granular cast were seen in the urinary sediment. Repeated analyses of the urine showed persistent alkalinity, the presence of protein (between 1-plus and 3-plus), negative and "1-plus" (green) reactions to Benedict's reagent, specific gravity 1.011 to 1.020, and total osmolarity 353 to 690 mOsm./L. Glucose was not demonstrated in the urine. The serum sodium level was 133 mEq./L.; potassium,

* From the Department of Pediatrics, Kaiser Foundation Hospital, Oakland, California.



FIG. 1. Photograph of the twins at age twenty-two months. R. H. on the left, D. H. on the right. See text for description of abnormalities and rate of growth and development.

4.5 mEq./L.; arterial blood pH, 7.32; chloride 112 mEq./L.; calcium, 10.3 mg./100 ml.; phosphorus, 4.6 mg./100 ml.; alkaline phosphatase, 17.5 King-Armstrong units per 100 ml. Blood Kahn, cephalin flocculation, total serum protein, albumin, globulin and serum bilirubin tests yielded normal results. The kidneys and urinary tract appeared normal on urographic examination, and nothing unusual was seen in roentgenograms of the skull and long bones. Iridectomy and linear extraction of the cataract in the left eye were performed and the infant was discharged.

Growth and development continued slowly. On November 26, 1956, at the age of three and a half months, the child was readmitted to the hospital in an attempt to elucidate the nature of his metabolic disorders. There was evidence of excessive aminoaciduria involving most of the common amino acids, intermittent proteinuria, hyperphosphaturia, alkaline urine, and metabolic acidosis.

Beginning on November 29, 1957, sodium citrate was given in a quantity equivalent to 10 mEq. of sodium daily. The dosage of vitamin D was 1,000 units daily. The sodium citrate was increased to 30 mEq. daily at age ten months, to 45 mEq. daily at age twelve months, and to 60 mEq. daily at age twenty months. The infant has gained steadily but slowly in height and weight. No evidence of rickets was seen in roentgenograms of the upper and lower extremities at age eighteen months. Glaucoma was present in the right eye; in the left, there was evidence of scar tissue filling the iridectomy coloboma. At age eighteen months iridectomy was performed on the right eye and ocular tension was reduced. At age twenty-one months needle biopsy of the right kidney and surgical biopsy of the right fifth costochondral junction were performed. At age twenty-two months (Fig. 1) the infant had twelve teeth and gazed at bright lights; he could sit alone, roll over, crawl, stand with aid, and repeat a few simple sounds.

CASE II. D. H. was delivered, by external version and extraction, thirty minutes after his twin brother on August 3, 1956. The placenta contained two amnions and two chorions. The infant's birth weight was 5 pounds, 15 ounces. At birth he was limp and cyanotic, but respiration occurred immediately and spontaneously, and his color improved after he had been in an incubator for two hours. There was no further neonatal difficulty, and the infant was discharged at the age of seven days, weighing 5 pounds, 4 ounces.

He was brought to the clinic with his brother at age seventeen days, having failed to gain weight on a diet consisting of an evaporated milk formula, vitamin D (1,000 units daily), and an iron preparation supplying

15 mg. iron daily (Fer-in-Sol® 0.6 ml.). The physical findings were similar to those observed in his twin brother, although he was smaller than his sibling, weighing 5 pounds, 6 ounces at age seventeen days. There were bilateral corneal opacities, prominent epicanthal folds, high palate, tapered fingers, hyporeflexia and a scaphoid skull. The infant preferred to lie in an opisthotonic position, but his neck could easily be flexed. The ophthalmologist noted bilateral congenital cataracts with posterior synechiae; the pupils dilated to 3.2 mm. following instillation of 1 per cent atropine, and tension in each eye was 28 mm. of mercury.

At three and a half months of age the patient was admitted with his sibling for further study. He was small and thin, and did not follow a bright light with his gaze. His muscle tone was poor and the extremities were hyperextensible. His weight was 8 pounds, 12 ounces; height, 21 inches; head circumference, 15½ inches; chest circumference, 14 inches. The anterior fontanelle measured 2 inches in length and 1½ inches in width. The eye findings were unchanged.

On admission, the leukocyte count was 12,600/cu. mm. with a normal differential count; the erythrocyte count, 4.8 million/cu. mm. The erythrocytes exhibited hypochromia and microcytosis on smear. The urinary specific gravity varied between 1.015 and 1.025; total osmolarity, between 341 and 990 mOsm./L. The urine contained protein (1-plus), no sugar or acetone, and reacted positively (2-plus) to the Sulkowitch test. Occasional granular casts were seen in the sediment. Qualitative tests of the urine for cystine yielded negative, 2-plus and 3-plus reactions on three occasions. The urinary protein content, as measured by the Esbach test, was 0.1 gm./100 ml. on two occasions. Reactions to repeated qualitative tests for protein varied between 1-plus and 3-plus, and for reducing substance between 0 and 2-plus. Glucose was not present in the urine. The pH of the arterial blood was 7.24. The carbon dioxide-combining power of the blood was 20.5 mEq./L.; sodium, 129 mEq./L.; calcium, 10.2 mg./100 ml.; inorganic phosphorus, 4.3 mg./100 ml.; urea nitrogen, 15 mg./100 ml.; fasting blood sugar, 135, 99 and 108 mg./100 ml. on three occasions; total protein, 7.2 gm./100 ml.; albumin, globulin, 3.7/2.5 gm./100 ml.; and serum creatinine 1.33 mg./100 ml.

On November 29, 1956, the administration of sodium bicarbonate was begun, in a dosage equivalent to 10 mEq. of sodium daily (a quantity equimolar to the quantity of sodium citrate administered to the brother). The daily dose of vitamin D (1,000 units) was continued; iron medication was withdrawn. The diet consisted of an evaporated milk formula and strained foods. The dosage of sodium bicarbonate was gradually increased concomitantly with increments in sodium citrate dosage to the twin, until the infant was one year old. Then, on August 14, 1957, the medication was changed to sodium citrate (30 mEq. daily), because of the comparative ease of administration of this substance. The dosage was increased to 45 mEq. at age sixteen months, and to 60 mEq. at age twenty months.

This infant's growth and development paralleled that of his brother, but was slower. Teething began at the age of six months, and fourteen teeth were present at age twenty-two months. The daily dose of vitamin D was increased to 3,000 units at thirteen months of age and to 4,500 units at age sixteen months (an amount 4.5 times that received by his twin). Roentgenograms taken at the age of eighteen months showed no evidence of rickets. At age twenty-one months biopsies were performed on the right kidney and the right fifth costochondral junction. Iridectomy and linear extraction of the cataract in the left eye were performed at age seven months. The tension in each eye prior to operation was 55 mm. of mercury. Operations performed on the right eye included iridencleisis, cyclodiathermy, goniotomy, and iridectomy and cataract extraction.

METHODS

Sodium and potassium levels were determined by flame photometry. The following substances were analyzed in the serum and/or the urine: inorganic sulfate [*3*], organic acids [*4*], titratable acidity [*5*], ammonia nitrogen [*6*], creatinine [*7*], chloride [*8,9*], inorganic phosphorus [*10*], urea nitrogen [*11,12*], calcium [*13*], and alkaline phosphatase [*14*]. Alpha-amino nitrogen determinations in serum and urine were performed by Dr. Harold A. Harper [*15,16*], of the University of California. Urinary amino acids were determined microbiologically [*17*] through the courtesy of Commander Paul Doolan, Oak Knoll Naval Hospital. Urine chromatographic studies were performed by Dr. C. E. Dent, University College Hospital Medical School, London. Total osmolarity was determined by means of a freezing point depression method (Fiske osmometer) [*18*]. At age twenty-two months, needle biopsy of the right kidney and surgical biopsy of the right fifth costochondral junction were performed in each infant by Dr. Carolyn Piel, Department of Pediatrics, Stanford University Medical School. Electron microscopic study of the renal biopsy material was performed by Dr. Joseph Goodman, Long Beach Veterans Administration Hospital, Long Beach, California. Renal biopsy tissue had been fixed in 1 per cent osmic acid buffered to pH 7.4 and imbedded in methacrylate.

Normal values for some of the less commonly determined substances, using the analytic methods described, are as follows: Urinary ammonia nitrogen: 0.70 gm. (50 mEq.)/day in the adult [or about 0.41 gm. (29 mEq.)/sq. m./day], usually comprising about 4 per cent of the urinary nitrogen and increasing up to tenfold during acidosis. Titratable acidity: about 0.2 to 0.8 mEq./kg./day. Urinary alpha-amino nitro-

TABLE I

URINE EXCRETION VALUES

Date	Age (mo.)	Medication	pH	Sodium (mEq./sq. m./day)	Potassium (mEq./sq. m./day)	Chloride (mEq./sq. m./day)	Inorganic Phosphorus (mg./sq. m./day)	Calcium (mg./sq. m./day)	Ammonia Nitrogen (mg./sq. m./day)	NH_4N/Urea Nitrogen (%)	Titratable Acidity (mEq./kg./day)
R. H., Twin No. 1											
11/27/56	3½	.....	7.5	30.0	37.9	99.6	1220	34.0	....	....	....
11/28/56	3½	.....	8.0	26.8	37.9	100.8	1216	35.5	....	....	....
11/29/56 to 8/6/57	....	Na citrate 10–30 mEq./day	...	....	.....	.....	....	.....	....	....	....
8/6/57	12	.....	6.8	61.8	50.1	34.3	773	50.9	247	4.9	....
8/7/57/to 8/12/57	....	NH_4Cl 30 mEq./day	...	....	.....	.....	....	.....	....	....	....
8/12/57	12	.....	5.9	23.9	50.7	52.2	842	51.2	380	5.5	1.36
8/12/57 to 2/10/58	....	Na citrate 45 mEq./day	...	....	.....	.....	....	.....	....	....	....
2/10/58	18	.....	7.6	...	70.1	55.6	1400	58.5	156	1.6	....
2/10/58 to 2/17/58	....	NH_4Cl 50 mEq./day	...	....	.....	.....	....	.....	....	....	....
2/17/58	18	.....	6.8	...	101.0	92.4	1965	160.0	891	4.7	1.25
D. H., Twin No. 2											
11/27/56	3½	.....	8.0	31.6	31.7	74.2	1290	27.1	....	....	....
3/12/57 to 8/6/57	....	$NaHCO_3$ 12.5–30 mEq./day	...	....	.....	.....	....	.....	....	....	....
8/6/57	12	.....	7.1	68.4	57.8	31.5	834	58.7	329	6.2	....
8/7/57	12	.....	7.0	61.5	49.4	46.8	761	51.3	462	9.8	....
8/7/57 to 8/12/57	....	NH_4Cl 30 mEq./day	...	....	.....	.....	....	.....	....	....	....
8/12/57	12	.....	6.0	17.8	44.5	42.6	858	35.8	488	7.4	....
8/14/57 8:35 A.M. to 10:05 A.M.	....	Phosphate buffer pH 7.45 135 ml. intravenously	...	....	.....	.....	....	.....	....	...	....
8/14/57	12										
7:00 A.M.	....	.....	...	....	.....	.....	....	.....	....	....	....
10:25 A.M.	....	.....	5.7	66.8	77.9	45.8	2915	66.5	401	5.8	4.26
12:30 P.M.	....	.....	5.9	83.3	60.1	37.8	2810	....	620	....	3.73
4:40 P.M.	....	.....	6.5	52.6	26.7	38.4	1172	75.9	1070	22.8	1.04
8/15/57 to 2/10/58	....	Na citrate 45 mEq./day	...	....	.....	.....	....	.....	....	....	....
2/10/58	18	.....	6.8	....	85.5	61.0	1288	57.3	224	1.7	1.03
2/10/58/to 2/17/58	....	NH_4Cl 50 mEq./day	...	....	.....	.....	....	.....	....	....	....
2/17/58	18	.....	6.8	....	101.0	94.0	1700	253	794	4.5	1.04

gen: about 2 mg./kg./day for this age group. Serum alpha-amino nitrogen: (fasting) 4 to 6 mg./100 ml. Organic acids: about 1 mEq./kg./day. Serum alkaline phosphatase: 5 to 20 King-Armstrong units/100 ml.

In order to minimize the changes occurring with increasing size of the subjects, the urinary excretion values are expressed in terms of body surface area and/or body weight wherever possible.

Since total urinary non-protein nitrogen was not determined, urinary ammonia nitrogen values are expressed in terms of percentage of the urinary urea nitrogen.

RESULTS

Urine and serum studies in these fraternal twins are summarized in Tables I and II. Urine studies yielded the following information: (1) marked aminoaciduria involving most of the common amino acids, (2) a tendency to excrete an alkaline urine, (3) proteinuria and intermittent cylindruria, and (4) diminished ability to increase the excretion of ammonia and titratable acid following ammonium chloride administration. Although balance studies were not performed, the urine excretion values for phosphorus (over 1.0 gm./sq. m./day) and potassium appear to be abnormally high, and those for calcium (about 50 mg./sq. m./day) seem low.

The urinary excretion of alpha-amino nitrogen was much increased, varying between 13 and 40 mg./kg./day in D. H., and between

TABLE II
SERUM VALUES

Date	Age (mo.)	Medication	pH	CO_2 (mEq./L.)	Na (mEq./L.)	Cl (mEq./L.)	K (mEq./L.)	Ca (mg. %)*	P (mg. %)*	Alkaline Phosphatase (K-A u./100 ml.)
R. H., Twin No. 1										
11/27/56	3½	0	....	18.5	135	102	5.0	10.0	3.9	24
12/14/56	4	0	7.32	14.0	...	...	...	....	....	....
8/6/57	12	Na citrate	....	17.5	...	...	...	....	4.7	21
8/13/57	12	NH_4Cl 30 mEq./day	....	19.5	...	110	...	....	4.5	....
2/10/58	18	Na citrate	7.40	14.8	142	112	3.9	11.0	5.0	6.5
2/17/58	18	NH_4Cl 50 mEq./day	7.22	15.4	144	115	3.7	....	....	16.0
D. H., Twin No. 2										
11/27/56	3½	0	....	20.5	129	104	4.9	10.2	4.3	29
1/15/57	5	0	....	21.4	...	115	...	8.9	5.0	30
8/6/57	12	$NaHCO_3$	....	20.0	...	...	...	....	4.5	18
8/13/57	12	NH_4Cl 30 mEq./day	....	21.8	...	109	...	....	4.4	....
8/14/57	12	Phosphate buffer	....	21.8	...	105	...	10.0	11.3	....
2/3/58	18	Na citrate	....	....	...	...	...	....	5.4	15.0
2/10/58	18	Na citrate	7.39	19.4	142	110	4.3	10.6	5.7	11.0
2/17/58	18	NH_4Cl 50 mEq./day	7.29	13.8	142	114	4.2	....	....	18.5

* (mg. %) = (mg./100 ml.).

13 and 24 mg./kg./day in R. H. Microbiologic assay revealed abnormally large amounts of all of the common amino acids (Table III) with the exception of leucine, isoleucine and valine, which were excreted in quantities similar to those excreted by the control subject. Chromatographic assay gave comparable results. The fasting serum levels of alpha-amino nitrogen were slightly below normal in both infants. Slit lamp and bone marrow examinations failed to reveal evidence of cystinosis.

Total organic acids were present in the urine in slightly greater than normal amounts (1.4 mg./kg./day in D. H. and 2.2 mg./kg./day in R. H.). The values for urinary ammonia nitrogen and titratable acid excretion would be considered normal in the absence of systemic acidosis, but are abnormally low for the subject with acidosis.

The creatinine clearance was normal in each infant (68 ml./sq. m./minute in D. H. and 87 ml./sq. m./minute in R. H.). The values for urea clearance were 50 ml./sq. m./minute in D. H. and 54 ml./sq. m./minute in R. H.

Prior to therapy with alkali, systemic acidosis and elevation of the serum alkaline phosphatase level were observed.

Sodium, in the form of citrate or bicarbonate, was administered to both infants beginning at the age of three and a half months, and the dosage was gradually increased with their age. (Table I.) After base therapy was begun, the following alterations were observed in the urine: the excretion of chloride diminished and the

TABLE III
RESULTS OF MICROBIOLOGIC STUDIES OF URINARY AMINO ACID EXCRETION OF TWINS MADE AT AGE FIVE MONTHS*

Common Amino Acids	R. H., Twin No. 1	D. H., Twin No. 2	A Three Year Old Normal Child
Alanine	91	58	1.5
Arginine	28	25	2.8
Aspartic acid	8.9	11.5	1.1
Cystine	42	36	10.4
Glutamic acid	4.4	4.1	Nil
Glutamine	140	144	11.6
Glycine	77	117	41
Histidine	121	122	49
Isoleucine	1.5	1.0	1.7
Leucine	4.2	4.4	1.5
Lysine	185	233	2.2
Methionine	1.9	2.8	0.2
Phenylalanine	10.5	108	3.4
Proline	81	39	10
Serine	77	94	5.2
Threonine	91	92	1.6
Tryptophane	12.1	10.0	6.4
Tyrosine	33	33	6.1
Valine	6.3	4.6	4.3

* Values (expressed in mg./day) are compared with those of a normal three year old child.

excretion of sodium and potassium rose. The pH decreased slightly during the early months of treatment, but later rose to pretreatment levels in one of the twins (R. H.). Phosphorus excretion decreased slightly initially but at age eighteen months was at levels approximating those before treatment. The excretion of ammonia, titratable acid and alpha amino nitrogen was apparently not affected.

There was a gradual decrease in serum alkaline phosphatase during the course of therapy. (Table II.)

Ammonium chloride was administered to both infants on two occasions, once at age twelve months in a dosage of 30 mEq./day for seven days, and again at age eighteen months in a dosage of 50 mEq./day for seven days. (Tables I and II, Fig. 2.) The following effects were observed: (1) In the serum: decrease in pH; rise in alkaline phosphatase, chloride and blood urea nitrogen; no significant change in the other components studied. (2) In the urine: a. Increase in the excretion of calcium, phosphorus, chloride and urea; only slight increase in the excretion of ammonia (this rise was much less than the normal response to ammonium chloride [*19–23*]); no significant change in excretion values of organic acids (which were slightly high initially). b. No significant change in pH or titratable acidity.

At age twelve months, D. H. received 135 ml. of sodium phosphate buffer (pH 7.45) intravenously over a period of ninety minutes. (Table I, Fig. 2.) The urinary excretion of phosphorus and the serum inorganic phosphorus level rose rapidly. The urine titratable acidity, ammonia excretion values and ammonia/urea nitrogen ratio increased to a degree greater than that which had followed the administration of 50 mEq. of ammonium chloride daily for seven days. (Table I, Fig. 2.) Renal mechanisms which may account for these results will be discussed.

No change in the rate of growth was evident between the ages of three and a half and nine months. At age nine months the rate of growth apparently accelerated in both infants (Fig. 5), coincident with the increase of sodium citrate and bicarbonate dosage to 20 mEq./day. Both infants received vitamin D in a dosage of 1,000 units daily until thirteen months of age. The amount administered to D. H., the smaller of the two, was then augmented until by age sixteen months he was given 4,500 units daily. The larger dose did not alter his rate of growth or laboratory results as compared to those of his twin.

BIOPSY RESULTS

Biopsy of the right sixth costochondral junction and needle biopsy of the right kidney were performed in each infant at age twenty-two months. Microscopic examination of the bone showed normal calcification and ossification of the cartilage. Renal tissue in each case showed normal appearing glomeruli; the renal tubules were arranged in a normal fashion and showed occasional multinucleated epithelial cells and unidentifiable crystalline material within the tubular lumens. The changes in the renal tubules were not considered to be characteristic of a specific disease. Further study by electron microscopy of the renal tissue from both infants revealed abnormalities which were mainly in the renal tubule cells. The mitochondria within the tubule cells were swollen and there was disruption of the mitochondrial cristae. (Fig. 3.) Sections through the glomeruli revealed no abnormalities except for swelling of the foot processes. (Fig. 4.) Rhodin [*24*] described

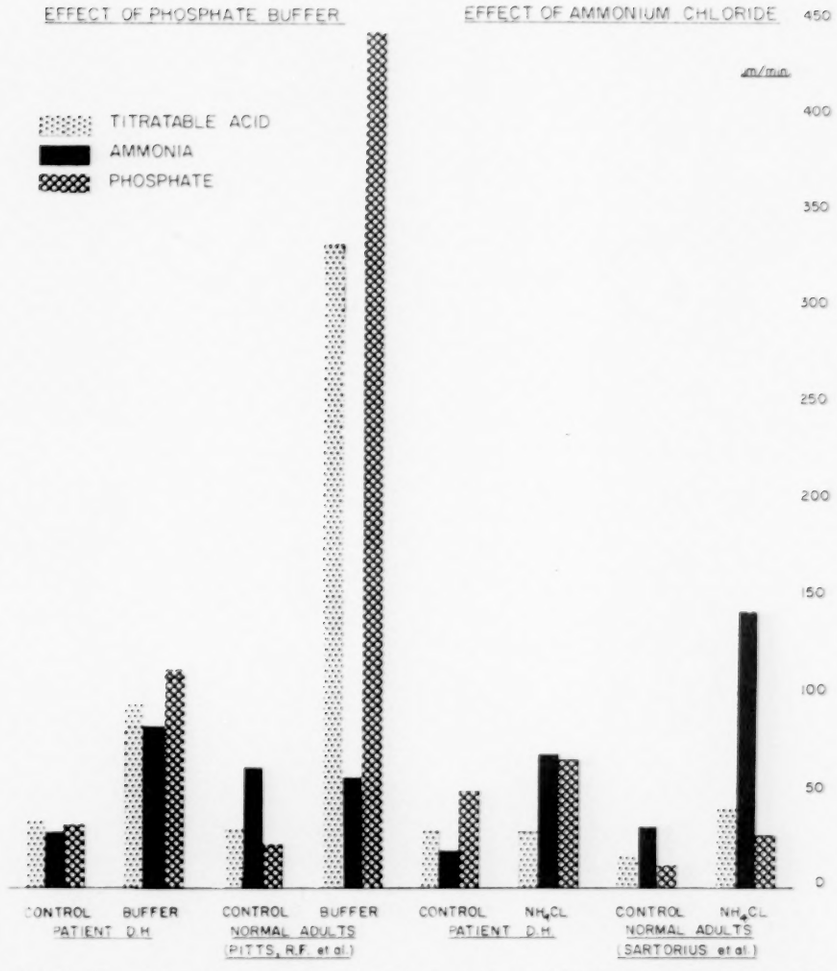


FIG. 2. The effect of administration of ammonium chloride and phosphate buffer to D. H., compared to the effect of administration of these substances to normal adult men (as observed by Sartorius et al. [*19*] and Pitts et al. [*23*]). All results expressed in terms of micromoles per minute per 1.73 sq. m. body surface area. See text for discussion.

autolytic changes in renal tubule cells of mice, including swelling of the mitochondria and destruction of the cristae, following a delay as brief as one hour in fixation of tissue.

The significance of the observations made by electron microscopy in these cases is questionable. There is a paucity of published descriptions of the electron microscopic appearance of renal biopsy material from normal human subjects. Swelling of mitochondria can occur in renal tissue obtained from such subjects [*25*] when current methods of obtaining, fixing and embedding the material are utilized.

COMMENTS

The findings in these double ovum twins are similar to those reported by Lowe and his coworkers in 1952 [*2*]. For the purposes of this discussion, the term "Lowe's syndrome" will be used to indicate a congenital disease manifested principally by aminoaciduria, hyperphosphaturia, proteinuria, decreased ability of the kidney to form ammonia and an acid urine, systemic acidosis, congenital cataracts with glaucoma, retardation of growth and development, and rickets (if alkali therapy is not instituted). The syndrome reported by Lowe included all of the salient features of Fanconi's syndrome; in addition, the kidney could not respond to acidosis by increasing the excretion of ammonia and titratable acid. Whereas Fanconi's patients excreted a highly acid urine containing a greater than normal amount of ammonia and titratable acid [*26*], the urine of Lowe's patients was alka-

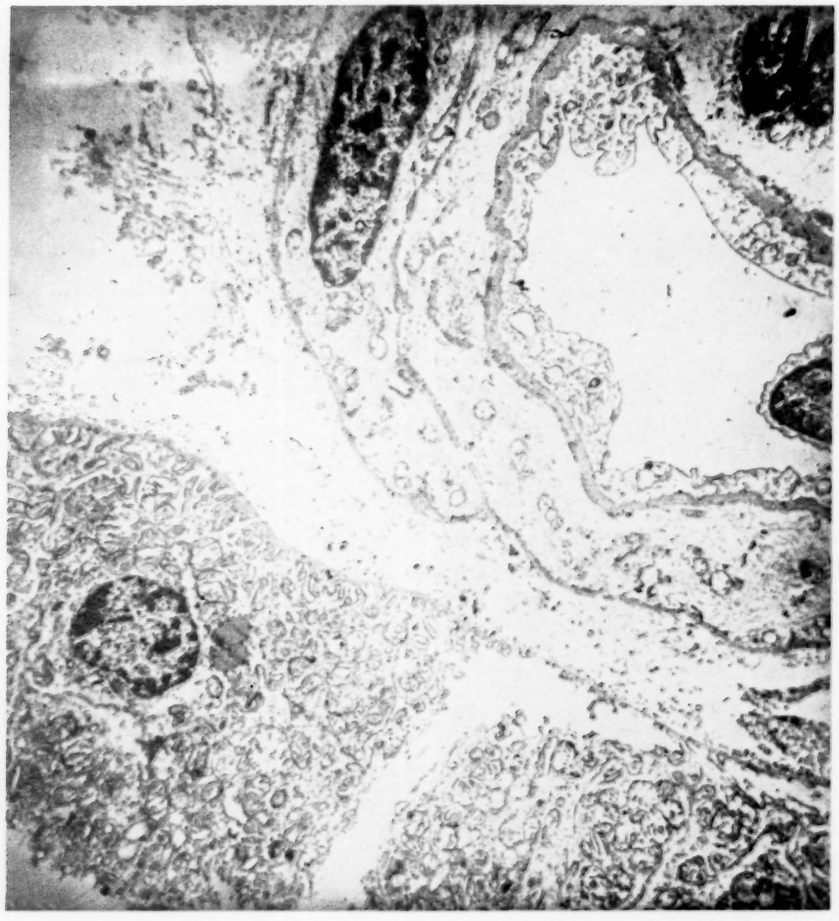


FIG. 3. Electron micrograph showing a tubule cell in the lower left hand portion with swollen and disrupted mitochondria. In the upper right hand portion is an interstitial blood vessel with an endothelial cell lining the vessel wall. Original magnification × 8,800 (courtesy of Dr. J. Goodman, Long Beach, California).

line or slightly acid. Such defects in the ability of the renal tubules to make ammonia and to acidify urine [*27,28*] was termed by Albright "renal acidosis" [*29*].

Systemic acidosis is present in both Lowe's and Fanconi's syndromes, but it is apparently produced by different mechanisms in the two diseases. In Lowe's syndrome the renal tubular acidosis described by Albright appears to be operative; the kidneys have a decreased ability to excrete an acid urine and to conserve base through the production of ammonia and hydrogen ions. Albright has expressed the belief that the chronic acidosis of Fanconi's disease "is due to an excess of organic acids being presented to the kidneys for excretion" [*29*]. Although Lowe considered organic aciduria (other than that due to aminoaciduria) to be an important manifestation of this syndrome, the levels of organic aciduria reported in his patients (1.3 to 6.4 mEq./kg./day) were not as elevated as those reported in the Fanconi syndrome [*26*]. In our patients the organic aciduria was only slightly higher than that reported in normal subjects and could largely be accounted for by the aminoaciduria.

The urinary loss of glucose which occurs in patients with Fanconi's syndrome was not observed in the infants herein described. Since infants with Fanconi's syndrome can compensate for the acidosis through renal mechanisms, one would anticipate that the acidosis in those persons would be less severe than in the twins presented.

Notwithstanding the difference between the mechanisms of production of systemic acidosis in the two syndromes, the effects of the chronic acidosis seem to be the same: available base is lost from the body. Since the preservation of sodium, the main cation of the extracellular

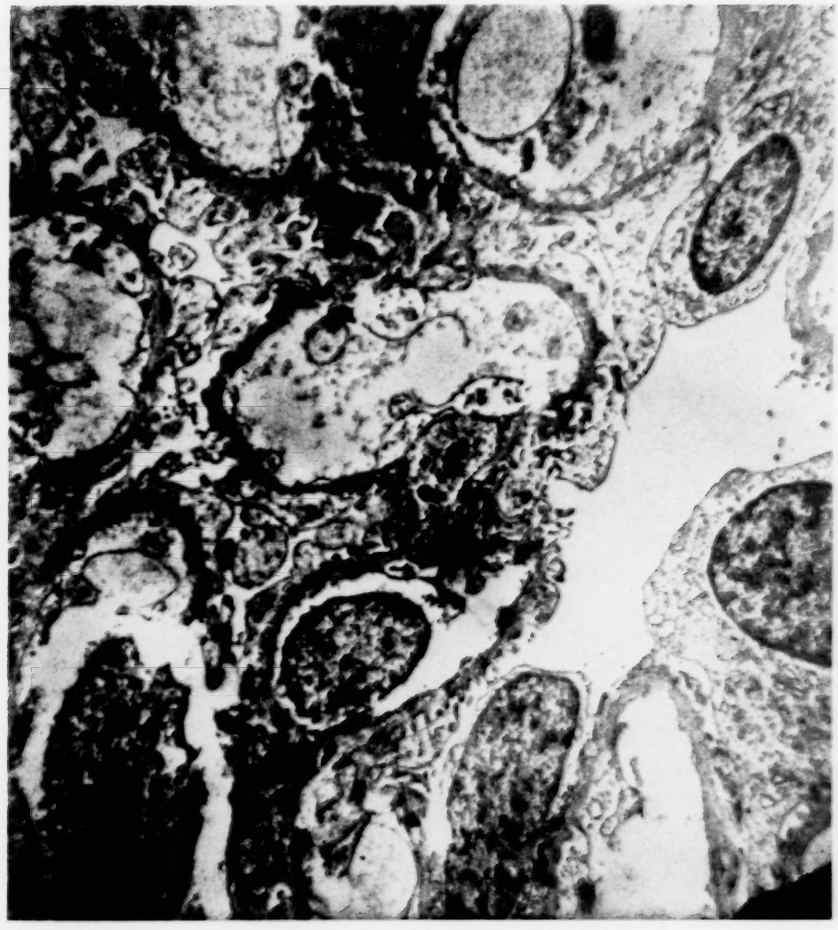


FIG. 4. Electron micrograph of a section through a glomerulus. The foot processes of the epithelial cells appear slightly swollen. Original magnification × 15,200 (courtesy of Dr. J. Goodman, Long Beach, California).

fluid, is a physiologic necessity, the response to chronic acidosis is an increase in the renal excretion of other body base, mainly calcium and potassium. The continued renal loss of calcium, together with the hyperphosphaturia, leads to osteomalacia, and increased potassium excretion results in depletion of body potassium.

McCune and his colleagues [*26*] expressed the belief that the hyperphosphaturia of Fanconi's syndrome was due largely to the diminished renal tubular reabsorption of phosphorus. It was Albright's opinion [*29*] that the increased urinary excretion of phosphorus in this syndrome could be ascribed mainly to secondary hyperparathyroidism, but he did not object strongly to McCune's concept. Our results constitute evidence in favor of McCune's hypothesis that the kidneys rather than the parathyroid glands are of primary importance in this disorder. Hypercalciuria was not present, and following the administration of alkali to our patients the hyperphosphaturia persisted in spite of the fact that the serum values of calcium, phosphorus and alkaline phosphatase remained normal.

The rapid intravenous administration of buffered phosphate resulted in a greater urinary excretion of ammonia and titratable acid than did the administration of ammonium chloride for one week. (Fig. 2, Table 1.) Similar results were observed following phosphate administration in patients with "renal hyperchloremic acidosis," in whom there is a decreased excretion of ammonia and titratable acid in the urine [*20,22*]. Schiess and his co-workers [*30*] have shown that in normal subjects the excretion of titratable acid in the urine is directly proportional to the amount of buffer appearing in the urine when phosphate buffer is administered. Also, it has been found that during the first few hours following the administration of an acidify-

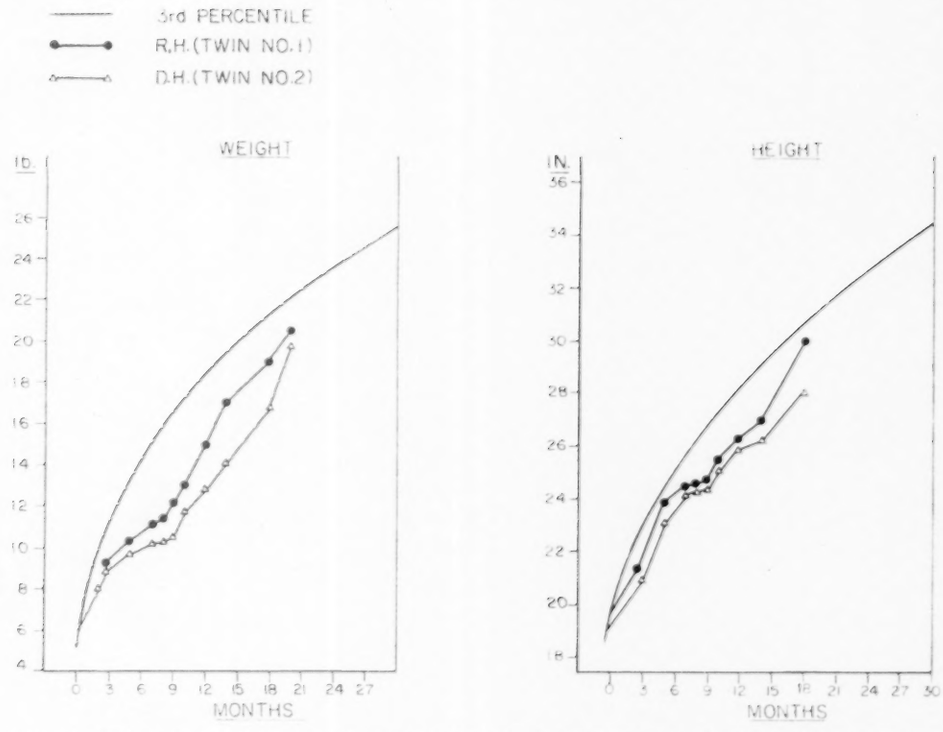


FIG. 5. Rate of increase in growth in both infants. Height and weight changes are plotted against the third percentile curve for age.

ing salt, ammonia and titratable acid excretion increase at equivalent rates [*19*]. Since phosphate buffer has a pKa of about 6.7, its administration can lead to increased hydrogen ion and, secondarily, to increased ammonia excretion without decreasing urinary pH. But following the administration of an acidifying salt such as ammonium chloride, the urinary pH falls with the increased excretion of titratable acid and ammonia. Thus, in these patients with diminished renal acidification, phosphate buffer presents a unique stimulus to the renal tubules.

It is conceivable that the decreased renal excretion of ammonia and titratable acid that is observed in the clinical syndromes encompassing renal tubular acidosis results from a deficiency or inhibition of the enzyme carbonic anhydrase. The administration of carbonic anhydrase inhibitor to normal persons leads to decreased renal excretion of ammonia and titratable acid, decreased tubular reabsorption of bicarbonate, increased urinary excretion of potassium, alkalinization of the urine, and systemic acidosis [*31*], all of which are present in patients with renal tubular acidosis. However, adults exhibiting renal tubular acidosis have responded in a normal fashion when an inhibitor of carbonic anhydrase was administered [*32*], implying that this enzyme is not the main defect limiting urine acidification in the entity under consideration. The fact that in our patients the renal excretion of ammonia and titratable acid could increase, particularly when phosphate buffer was administered, would appear to indicate some degree of carbonic anhydrase activity. Recently there has been interest in the renal tubular transport of sodium as the stimulus for urine acidification [*33,34*]. Evidence has been adduced that sodium undergoes active cellular absorption [*34–36*], leading to the passive diffusion of chloride ion into, and of hydrogen ion out of the cell. Pitts [*34*] has suggested that there exists in the distal tubule a "coupled ion" effect, with competition between hydrogen and potassium ions for the sodium exchange mechanism. Although experimental evidence is lacking, it is interesting to hypothesize that in renal tubular acidosis there is a defect in the "sodium pump" in the renal tubular cells, which leads to decreased excretion of titratable acid and ammonia, increased bicarbonate excretion, and systemic acidosis.

Aminoaciduria was constantly observed in the twins presented. That the blood level of alpha-

amino nitrogen was not elevated suggests a renal basis for the increased urinary excretion of the amino acids.

Since our patients show no evidence of diminished glomerular function (creatinine clearance and blood urea values are normal), their renal abnormalities appear to be of tubular function.

The abnormal renal excretion of such solutes as amino acids, phosphate, ammonium and titratable acid, and the defect in the sodium pump may be due to a congenital diffuse abnormality in enzymatic activity within the renal tubule cell. The chief abnormality observed under the electron microscope in these patients was swelling and distortion of the mitochondria in the renal tubule cells. Most tubular cell enzymes are probably in the mitochondria [*37*], and the fine structure of the mitochondrion appears to be essential to normal enzymatic activity [*24*]. But two points prevent us from attempting to correlate the chemical abnormalities observed with the electron microscopic findings: (1) it is hazardous to attempt to correlate structural changes with alterations in body tissue function, and (2) it is possible that in these cases the changes noted in the renal tubule cells on electron microscopy were artefacts inherent in current technics.

The significance of the thickening of the foot processes in the glomeruli is difficult to assess. Both of these infants exhibited proteinuria. Proteinuria is also a major manifestation of nephrosis, and changes similar to these (but more advanced) have been described in the glomerular podocytes in nephrosis [*38*].

Lowe [*2*] noted that the infants observed by him incurred rickets while receiving ordinary doses of vitamin D (1,000 to 2,500 units daily). The administration of alkali without increasing the dosage of vitamin D was followed by healing of the bones, emphasizing that the rickets was not "vitamin resistant." Similarly, rickets did not develop in our patients following the administration of alkali and 1,000 units of vitamin D daily.

The fact that the patients are double ovum twins with no history of similar disorders in three generations of the family speaks against a hereditary basis for the syndrome. It appears more likely that some insult early in fetal life, which affected the kidneys and the other organ systems developing at that time, could have resulted in these diffuse anomalies.

On the basis of current knowledge, the congenital cataracts and glaucoma that were present in both twins can be explained only as developmental defects. Lenticular opacities occur in association with hypocalcemia in hypoparathyroidism and in sprue [*28*], but these infants were not hypocalcemic during the period over which they were observed. Hypotonicity and hyperextensibility of the extremities have been described in association with hyperparathyroidism [*28*], and some degree of secondary hyperparathyroidism may have been present in these infants. Following surgical procedures which included iridencleisis, cyclodiathermy, goniotomy, iridectomy and cataract extraction, at the age of eighteen months both infants were believed to have light perception. The other anomalies noted on physical examination are best explained as congenital defects.

SUMMARY

Double ovum twins are reported who have abnormal renal excretion of certain solutes, most notably ammonia, hydrogen ions, phosphate and amino acids, probably on the basis of disturbed renal tubular function. In both infants, electron microscopy shows abnormalities in the mitochondria of the renal tubular cells. Also present are other congenital defects including cataracts and glaucoma. Growth and development are retarded.

Since the findings are similar to those in three cases reported by Lowe and his co-workers [*2*], it has been found convenient to refer to this group of defects as "Lowe's syndrome." It is suggested that the disease is not familial, and that all of the defects are probably developmental abnormalities.

Alkali was administered from the age of three months; rickets did not occur.

The discussion is centered chiefly upon the renal defects and the relationship of the cases presented to Fanconi's syndrome.

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Coarctation of the Abdominal Aorta with Stenosis of the Renal Arteries and Hypertension*

Clinical and Pathologic Study of Two Cases and Review of the Literature

ALBERT A. BRUST, M.D., JOHN M. HOWARD, M.D., MILTON R. BRYANT, M.D.
Cincinnati, Ohio *Philadelphia, Pennsylvania* *Atlanta, Georgia*
and JOHN T. GODWIN, M.D.
Atlanta, Georgia

ALTHOUGH coarctation of the thoracic aorta is a well recognized entity which produces characteristic diagnostic signs, congenital coarctation of the abdominal aorta has received little attention because of its apparent rarity. Within a six-month period, we had the opportunity to study two young patients with severe hypertension associated with stenosis of the aorta and renal arteries in whom necropsy was performed. Because of the experiences with the first patient a correct clinical diagnosis was made antemortem in the second. Both patients had a systolic murmur and thrill over the upper part of the abdomen and lumbar spine, hypertension in the legs equal to or higher than that in the arms, and equal and forceful arterial pulses in the lower extremities. The ribs were not notched and collateral circulatory channels were not apparent.

This report with a review of the literature is written in the belief that a wider appreciation of the clinical features which these patients may present will permit more frequent recognition of this abnormality and the planning of appropriate surgical therapy.

CASE REPORTS

CASE 1. A fourteen year old schoolboy was admitted to the hospital for evaluation of severe hypertension of five years' duration.

At nine years of age he had complained of recurring morning headache, nausea and vomiting. At that time hypertension was discovered; the blood pressure was 190/140 to 230/180 mm. Hg and persisted in this range. Subsequently he was carefully studied in several hospitals and remained under constant medical observation. Tests for pheochromocytoma, repeated pyelograms and renal function tests failed to clarify the nature of the hypertension, and antihypertensive agents did not reduce the blood pressure. Physical development had proceeded normally and he remained active in athletics. For the past three years he had complained only occasionally of headache.

Family history revealed that both paternal grandparents had hypertension. The patient's mother, forty-seven years of age had asymptomatic benign hypertension.

Physical examination revealed a well developed teenage boy. The blood pressure was 240/140 mm. Hg in the right arm, 255/160 mm. Hg in the right leg, 250/145 mm. Hg in the left arm and 240/150 mm. Hg in the left leg. The pulse rate was regular at 80 per minute. Funduscopic examination revealed marked arterial spasm and a few arteriovenous compressions. The heart was slightly enlarged to the left and the cardiac sounds were booming in quality. A grade 1 blowing systolic murmur was heard over the precordium, loudest between the pulmonic and secondary aortic areas. It was not transmitted. A forceful systolic thrill was felt over the abdominal aorta, and a loud systolic murmur was heard over the same area with maximal intensity at the umbilicus and transmission into the femoral arteries. The murmur

* From the Departments of Medicine and Surgery, Grady Memorial Hospital and the Department of Pathology, St. Joseph's Infirmary, Atlanta, Georgia, and The Kettering Laboratory, Cincinnati, Ohio. Certain of the studies included in this report were supported by grants from the U. S. Public Health Service, the Georgia Heart Association, and the American Heart Association.

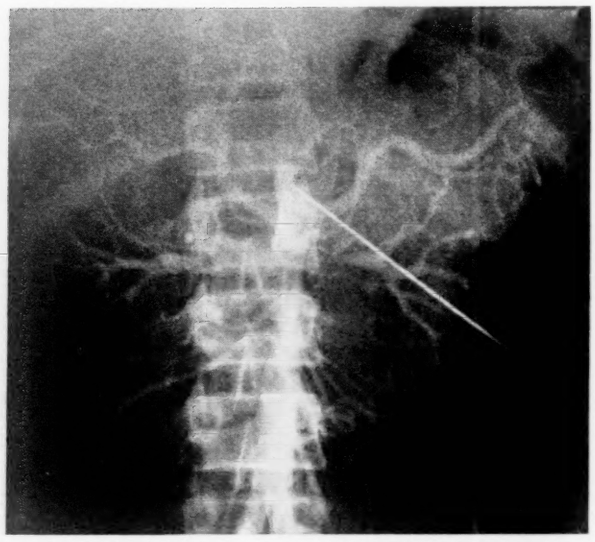


FIG. 1. Translumbar aortogram in Case 1. Prominent wedging of the left renal artery is present and the aorta is suspiciously narrowed just distal to the origin of the renal arteries. Bilateral stenosis of the renal arteries in association with coarctation of the abdominal aorta was ultimately demonstrated. In retrospect the right renal artery also appears suggestively wedged.

was heard also over the back, loudest over the lumbar spine. The femoral pulses were equal and forceful. Popliteal, posterior tibial and dorsalis pedis pulses were similarly strong.

The serological test for syphilis was negative and hematologic studies were within normal limits. Urinalyses were repeatedly negative with the random specific gravity ranging up to 1.023. The blood urea nitrogen was 12 mg. per cent. Phenolsulfonphthalein excretion was 40 per cent in twenty minutes and 75 per cent in two hours. Roentgenograms of the chest revealed no notching of the ribs, but the left ventricle was moderately enlarged, and left ventricular hypertrophy was indicated by the electrocardiogram. Intravenous pyelograms revealed no abnormality, dye clearance being noted bilaterally at five minutes. Retrograde pyelograms were likewise normal. No reduction in blood pressure resulted from the intravenous injection of Regitine,® tetraethylammonium chloride or hexamethonium.

Percutaneous translumbar aortography demonstrated a wedge-like constriction of the left renal artery and poor filling of the aorta immediately below the renal ostia. (Fig. 1.)

Because of these findings left nephrectomy and exploration of the upper abdominal aorta were performed through a modified left lumbar incision. Dissection of the left renal pedicle revealed the artery to be much smaller than normal with a point of constriction 1 cm. from its origin. A definite thrill could be felt over the renal artery at the site of constriction and distal thereto but no thrill could be palpated in the aorta. The aorta appeared somewhat narrowed distal to the renal outflow.

Following removal of the left kidney the blood pressure ranged from 220/130 to 290/180 mm. Hg, hemorrhages appeared in the optic fundi and heart failure supervened. The immediate postoperative period was complicated by atelectasis, moderate mediastinal emphysema and recurrent left hydrothorax. On the third postoperative day the bruit over the abdominal aorta again became audible and persisted.

Three weeks after discharge from the hospital he was readmitted with massive intracerebral hemorrhage, and died. The abdominal aorta and remaining right kidney as seen at necropsy are shown in Figure 2.

At autopsy, the thoracic aorta and its branches were normal. The opened aorta measured 3.4 cm. in circumference at the level of the diaphragm and diminished to 1.3 cm. at the level of the renal arteries. The celiac and superior mesenteric arteries revealed no abnormalities. The orifice of the left renal artery measured 1.5 mm. in diameter and that of the right renal artery was slightly smaller. Both arose immediately proximal to the point of greatest constriction of the aorta.

Distal to this point the aorta gradually increased to 2.6 cm. in opened circumference. The internal iliac arteries, lumbar arteries, and the venous system were normal. Each common iliac measured 1.9 cm. in circumference. The orifice of the inferior mesenteric artery measured less than 1 mm. in diameter.

The intima of the descending thoracic aorta showed diffuse atherosclerotic changes which were also seen to a lesser degree in the first portion of the abdominal aorta. Distal to the coarctation the intima appeared somewhat gelatinous.

The left kidney (specimen at nephrectomy) (Fig. 3.) weighed 178 gm. and appeared normal on gross examination. The renal artery in its proximal portion had a lumen reduced to 1 mm. diameter, and widened distally to 2.5 mm. The right kidney (specimen at necropsy) weighed 111 gm. The lumen of its artery was reduced by more than 50 per cent, and in addition the proximal portion contained a partially occluding thrombus. Histologic sections through the proximal portions of both renal arteries showed marked intimal proliferation and hyalinization, minimal fibrosis of the media, and extensive fibrous thickening of the adventitia. Distally, the arteries were normal. Sections through both kidneys revealed normal vessels and normal renal parenchyma.

Histologically, the ascending aorta showed minimal thickening of the intima and marked thickening of the media with medial cystic necrosis. The descending aorta demonstrated more marked intimal thickening with lipid deposits and cystic necrosis in the thickened media. Increased fibrous tissue was noted in the surrounding adventitia.

A definite formation of atheroma was noted in the



2 3

FIG. 2. Abdominal aorta opened from the rear together with remaining right kidney (Case I).

FIG. 3. View of the left renal hilus (Case I). The renal artery with its markedly reduced lumen is seen just superior to the end of the clamp.

intima of the diaphragmatic and proximal abdominal aorta together with partial destruction of the media and fibrosis and thickening of the adventitia. The media in numerous sections, beginning 2.8 cm. proximal to the celiac orifice, revealed a small dissecting aneurysm which had not perforated through the adventitia or back into the aortic lumen. It measured 1.3 cm. in width and 0.6 cm. in its thickest portion.

Sections through the coarctation demonstrated the progressive narrowing of this segment. The media was uniformly increased in thickness, and no constricting fibrous bands were evident. Medial cystic necrosis and fibrous thickening of the adventitia were present in sections proximal and distal to the coarctation. As the intima continued into the area of coarctation it became abruptly thickened by atherosclerotic plaques and distal to the coarctation it was extremely thick, containing a moderate amount of lipid material. Marked intimal proliferation narrowed the orifice of the inferior mesenteric artery, but the artery itself was normal. In the region of its bifurcation the aorta showed heavy intimal thickening but medial cystic necrosis was not evident.

Additional pathologic findings included diffuse atherosclerosis of the pulmonary and coronary arteries, cardiac hypertrophy (503 gm.), and intracerebral hemorrhage (left basal ganglia and left frontal lobe).

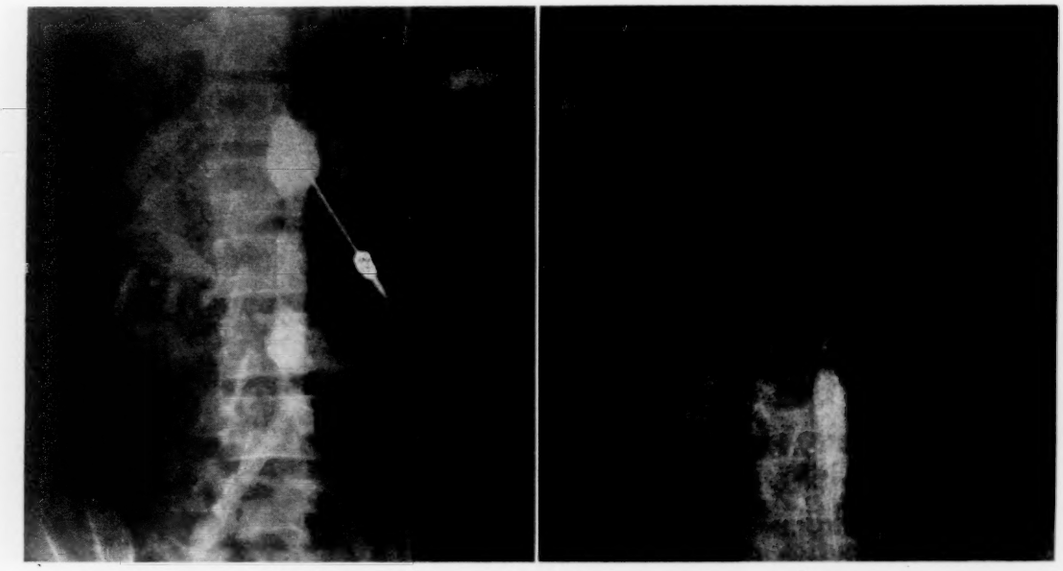
Comment: Left nephrectomy was performed in this patient in the erroneous belief that the renal artery stenosis was unilateral and that removal of an ischemic kidney might reduce the blood pressure. The dissecting aneurysm found at necropsy above the constricted segment of aorta apparently occurred during the postoperative period and presumably produced no clinical manifestations.

CASE II. A twenty-four year old white woman was admitted to the hospital with the chief complaint of severe headaches and dizziness.

She had been well until two years previously at which time she began having frequent morning headaches associated with dizziness, nausea and vomiting. The onset of these symptoms apparently coincided with the beginning of her fourth pregnancy. During this pregnancy hypertension was noted for the first time, and she received antihypertensive agents without obvious improvement.

After she was delivered of a normal male infant her systolic blood pressure was reported to range from 200 to 280 mm. Hg. and diastolic pressure 110 to 130 mm. Hg. Tubal ligation was performed three months postpartum and following this procedure her symptoms became progressively more severe.

Her family history was non-contributory for both hypertension and renal disease. Her mother and father were living and well at age forty-eight and fifty-three, respectively. She gave no history of scarlet fever, rheumatic fever, renal or venereal disease.



4 5

FIG. 4. Translumbar aortogram in Case II. Note the narrowing of the aorta at the approximate level of the renal arteries (not visualized). The abdominal aorta appears slightly dilated just proximal to the point of constriction.

FIG. 5. Retrograde aortogram in Case II. The catheter has coiled upon itself after meeting an obstruction above the renal artery level. Note the narrowed aorta and the marked stenosis of the proximal portion of the right renal artery. The left renal artery was not visualized.

Three previous pregnancies had been uncomplicated.

Physical examination revealed the blood pressure to be 276/134 mm. Hg in the right arm, 230/125 mm. Hg in the right leg, 250/120 mm. Hg in the left arm, and 240/135 mm. Hg in the left leg. Her pulse rate was 78 per minute and regular. Funduscopic examination showed attenuation and spasm of the retinal arteries and a few flame-shaped retinal hemorrhages. The heart was slightly enlarged to the left and a grade 2 systolic murmur was heard over the mitral and pulmonic areas. A loud systolic bruit and a palpable thrill were noted in the epigastric region and over the lumbar spine with transmission to the level of the bifurcation of the abdominal aorta. The femoral, popliteal, posterior tibial and dorsalis pedis pulses were equally as forceful as the corresponding pulses in the upper extremities.

Serological and routine hematologic studies were normal. Urinalyses were repeatedly negative, the specific gravity ranging up to 1.024. The non-protein nitrogen was 27 mg. per cent. Phenolsulfonphthalein excretion was 38 per cent in fifteen minutes and 60 per cent in two hours. Regitine and benzodioxane tests were negative and administration of ganglion-blocking agents failed to reduce the blood pressure. The electrocardiogram suggested left ventricular hypertrophy, and roentgenograms of the chest revealed enlargement of the heart to the left with no evidence of notching of the ribs. Intravenous pyelograms demonstrated bilateral excretion of the dye; however, at cystoscopy the flow of urine from the left kidney appeared to be reduced. Differential phenolsulfonphthalein studies showed 42 per cent of the injected dye to be excreted by the right kidney while only a trace was obtained from the left.

Percutaneous translumbar aortography with 35 ml. of 50 per cent Urokon® showed narrowing of the abdominal aorta for a distance of 3 cm. at the level of origin of the renal arteries. (Fig. 4.) Slight dilatation of the abdominal aorta immediately proximal to the narrowed segment also was noted. Although the renal arteries were not visualized, the renal shadows were well outlined and the left kidney was noted to be smaller than the right.

One week later in an effort to visualize the renal arteries a retrograde aortogram was attempted via the left femoral profunda artery. The catheter passed upward through the area of constricted aorta to the level of the first lumbar vertebra where it met an obstruction which caused its tip to coil. The injection of 50 ml. of 50 per cent Urokon again demonstrated narrowing of the abdominal aorta, and the right renal artery was visualized. (Fig. 5.) The proximal 1 cm. of the artery was narrowed to a diameter of 3 mm. with the remainder of the artery measuring 7 mm. in diameter.

To clarify the anatomic details relative to the left renal artery, the celiac and the superior mesenteric arteries, an antegrade aortogram was performed four days later while the patient was under sodium



6 7

FIG. 6. Abdominal aorta opened from the front (Case II) showing thickened constricted segment at the level of the stenosed renal arteries. The unusual valve-like structure arising from the posterior wall of the aorta is seen just above the area of coarctation.

FIG. 7. Enlarged view of the abdominal aorta (Case II) showing the 2 cm. cusp of the valve-like structure originating from the posterior wall. The blind pocket created by this structure blocked passage of the retrograde catheter (see Figure 5).

pentothal anesthesia. A cardiac catheter was inserted through the left brachial artery down to the level of the fifth thoracic vertebra and 50 ml. of 70 per cent Urokon was injected. Inadequate visualization of the descending aorta was obtained. During the procedure the patient's blood pressure remained at her usual hypertensive levels; however, postoperatively she failed to breathe spontaneously. Her pulse rate was regular at 70 per minute. For two hours the anesthesiologist manually assisted her respirations. She was then connected to a pneophore mechanical respirator, and at this point she became mentally alert, responding to her name and answering questions by appropriately shaking her head, but was unable to move her extremities. Neurological examination revealed evidence of cord damage at the level of C-2. Tracheotomy was performed, therapy with hydrocortisone and anticoagulants was begun and she was placed in an iron lung. Two hours later her blood pressure fell precipitously and cardiac arrest occurred. She died approximately twenty-four hours following the aortogram.

At autopsy the opened aorta, from arch to bifurcation, showed longitudinal wrinkling, yellow and greyish white areas of atherosclerosis and areas of calcification. The abdominal aorta was narrowed by a thickened, constricted segment beginning 2 cm. proximal to the origin of the renal arteries and extending 2 cm. distal thereto. (Fig. 6.) This area was surrounded by dense fibrous tissue. In addition, 4 cm. proximal to the level of the renal arteries the aortic lumen was markedly narrowed by a valve-like structure originating from the posterior aortic wall. (Fig. 7.) The "cusp" of this structure, measuring 2 cm., projected anteriorly and inferiorly into the aorta reducing its lumen to an anterior passage which measured only 0.8 cm. by 0.5 cm. The orifice of the celiac axis was completely occluded. The ostium of the superior mesenteric artery was located at the level of the free margin of the valve cusp and was moderately narrowed by thickened intima. The ostia of the renal arteries were markedly narrowed. The left renal artery would not admit a 1 mm. probe.

The left kidney weighed 120 gm. and on gross examination appeared normal although smaller than the right. The distal portion of its artery was normal but proximal sections showed marked thickening of the intima with almost complete obliteration of the lumen. The right kidney weighed 190 gm. Sections through the distal portion of its artery were normal,

but proximally the lumen was narrowed to 1 mm. by thickened intima. Histologic sections showed similar changes in both arteries with some destruction of the internal elastic lamina and thinning and disruption of the media with replacement by collagenous tissue. A mononuclear infiltrate with foci of hemosiderin was noted in the adventitia. The left kidney showed only mild atrophic changes in the tubules with an occasional glomerulus undergoing sclerosis. The right kidney was entirely normal.

The thoracic and proximal abdominal aorta showed marked thickening of the intima by fibrous plaques with calcification, and the media was extensively disrupted by young fibrous connective tissue with mononuclear cell infiltration. The thickened adventitia contained foci of lymphocytes and occasional multinucleated giant cells.

Valve-like Structure in the Abdominal Aorta. Sections from the base of the "valve" demonstrated an abrupt change in direction of the elastic fibers of the media such that the medial layer extended outward into the base of the valve itself. A few fine elastic fibers were noted in the central portion of the valve extending to the free margin. Sections from the posterior wall of the aorta at the level of the free margin of the valve showed a prominent defect or disappearance of the media corresponding to the extension of the media into the valve. This defect and the free edges of the valve showed heavy fibrous intimal layers. The adventitia was thickened throughout.

Abdominal Aorta in Area of Coarctation. The area of greatest intimal thickening was found to lie between the ostia of the renal arteries directly in the path of the "jet stream" of the coarctation. This fibrous thickening was in the form of a deposit or layer which could be separated from the underlying media by gentle force. The elastic tissue of the media was disrupted by foci of collagenous tissue and lymphocytic, plasma and giant cell infiltration. These inflammatory changes were limited to the outer third of the media and were marked in the greatly thickened adventitia.

Abdominal Aorta below Coarctation. Sections taken inferior to the coarctation showed only mild fibrous thickening of the intima. This change was strikingly less than that noted above the coarctation. The media appeared entirely normal.

Additional pertinent pathological changes were seen in the spinal cord where coronal sections at 3 to 4 mm. intervals revealed the arteries and veins to be patent. Hemorrhage and myelomalacia were noted at the level of the second, third and fourth cervical nerves. Microscopically there was loss of myelin in the lateral and anterior columns and between the posterior horns. Occasional ganglion cells had been destroyed, and interstitial hemorrhage and focal acute inflammatory changes were present.

Comment: It seems likely that this patient's death occurred because of reflux of contrast medium into the cerebral vessels during the attempt at antegrade aortography. Not only was her abdominal aorta circumferentially narrowed by coarctation at the level of the renal arteries but the unusual valve-like structure immediately proximal produced in addition a marked anteroposterior narrowing of the aorta. The high degree of intra-aortic obstruction thereby induced made it possible for the reflux of Urokon to occur.

COMMENTS

Except for the systolic bruit and thrill over the abdomen and lumbar spine the usual features of coarctation of the aorta were lacking in these two patients, and both had been thought to have essential hypertension. The remarkable similarity of physical signs and pathologic findings in both suggests that such a combination of manifestations deserves wider clinical recognition. Since both the aortic and renal artery lesions may be amenable to surgical correction this seems especially appropriate.

In both patients it appears likely that the severe hypertension was of the Goldblatt type, resulting from the narrowing of the renal artery lumens by intimal thickening extending from the aorta into the proximal portions of the renal arteries. In all respects this intimal proliferation conforms to the "jet lesion" described by Edwards et al. [*1*] in coarctation of the thoracic aorta and more recently elucidated in animal experiments by Rodbard [*2*]. The latter has demonstrated that the surgical narrowing of an artery induces rapid flow and the induction of intimal proliferation leading to progressive stenosis. In both these patients the ostia of the renal arteries lay directly in the path of the high velocity jet created by the coarctation.

Additional clinical and pathologic support can be found for the contention that the hypertension in these cases was the result of the production of bilateral Goldblatt kidneys by the narrowed lumens of the renal arteries. Favoring such an hypothesis are the youth of the patients, the extremely high diastolic blood pressure levels and the inability to reduce the blood pressure with autonomic ganglionic-blocking agents. The pathologic findings afford even more striking support in that the renal vasculature and parenchyma showed no evidence of hypertensive damage distal to the stenosed renal arteries. This damping of the brunt of the hypertensive impact by narrowed arterial lumens is one of the

characteristic pathologic features of the experimental Goldblatt animal and of a few cases in man.

The physical findings in the lower extremities, i.e., forceful arterial pulses and hypertension equaling or exceeding brachial blood pressures appear incompatible with the findings expected distal to a narrowed segment of aorta. It must be assumed that in these patients the degree of aortic obstruction produced by the coarctation while sufficient to produce the "jet stream phenomenon" was not enough to cause an appreciable blood pressure and pulse gradient in the lower extremities as compared to the upper.

REVIEW OF THE LITERATURE

In 1861 Power [*4*] described the first case of coarctation of the abdominal aorta which terminated fatally in a seventeen year old boy. At necropsy the abdominal aorta and iliac arteries were found to be diffusely constricted. Although no specific mention was made of the kidneys and renal arteries, hypertrophy of the left ventricle was interpreted as evidence of hypertension. When the clinical and pathologic findings of our two patients are combined with those from the literature, a total of seventeen cases become available for comparison purposes. Their findings are summarized in Table 1.

Two of the cases which have been included deserve special comment. In Fisher and Corcoran's patient [*5*] stenosis of both renal arteries was present, but the authors later expressed doubt as to whether or not the degree of aortic narrowing warranted the diagnosis of coarctation. In the case of Poutasse et al. [*6*] who reported successful homografting of bilaterally stenosed renal arteries, coarctation was not mentioned, but preoperative and postoperative aortograms showed persistent narrowing of the aorta at and distal to the renal arteries.

Clinical Data. The youthfulness of the patients reported is quite apparent from the Table. Fifteen of the patients in whom the information is available had their hypertension discovered or died within the first three decades of life. Blood pressure elevation was documented before age ten in three, before age twenty in seven, and before age thirty in five. Sex and race information were complete for thirteen patients, including eight females and five males. Eleven Caucasian, one Japanese and one Siamese patient were included.

Although all patients showed evidence of arterial hypertension, blood pressures have been compared only in those thirteen who had adequate arm and leg determinations. Brachial systolic pressures exceeded 200 mm. Hg in all patients except one, and diastolic levels ranged from 70 mm. Hg up to 180 mm. Hg. Femoral systolic pressures exceeded 200 mm. Hg in five patients and these showed a femoral diastolic range from 100 mm. Hg to 180 mm. Hg. The femoral systolic pressure equaled or exceeded the corresponding brachial pressure in five patients, and the femoral diastolic was the same or higher than the brachial diastolic in five. Diagnostically impressive systolic and diastolic pressure differences between arms and legs were obtained in only six patients, in three of whom leg pressures were unobtainable.

Information regarding pulses in the lower extremities was recorded in thirteen patients. Pulses were noted to be absent in five, diminished in four and normal in four. The latter three patients were among those who did not show arm-leg pressure differences.

A bruit usually described as systolic in time and harsh in quality was noted over the abdomen in nine patients and over the back in nine. A corresponding thrill was palpated over the abdominal aorta in both patients reported here and in one from the literature. In three cases from the literature a thrill was sought but not found. No mention of this sign is made in the others.

Information regarding rib notching or collateral circulation could be obtained in most of the reported cases. In only two patients was notching of the lower ribs demonstrated by roentgenogram, but collateral circulation in the lower thoracic region was noted in four others. The roentgenograms of ten patients showed no evidence of rib notching, but prominent intra-abdominal collateralization was ultimately demonstrated in four.

Detailed tests of kidney function were not reported with sufficient consistency in the cases from the literature to allow for accurate appraisal. It could be determined that at least twelve of the patients had normal urinalyses and that tests of concentration capacity and excretory function were uniformly within normal limits.

In five of the cases reported, the diagnosis of coarctation was established only at necropsy although it had been suspected in two of these. In three the condition was recognized at opera-

TABLE 1

CLINICAL AND PATHOLOGIC FINDINGS

Author	Date of Report	Age (yr.)	Sex	Race	Clinical Findings									Pathologic Findings			
					Blood Pressures mm. Hg		Femoral Pulses	Systolic Murmur		Systolic Thrill Abdomen	Rib Notching	Collateral Circulation	Diagnosis Established	Complications of Hypertension	Aortic Defect		Renal Artery Defect	Aortic Atherosclerosis
					Arm	Leg		Abdomen	Back						Nature and Site	Extent		
Power [4]	1861	17	M	W	.....	.....	.....	....	....	....	....	Thoracic	Necropsy	CVA†	Diffuse, distal to renal arteries	Aorta and iliacs constricted	.....	.....
Maycock [11]	1937	18*	F	W	200/89	130/110	Absent	Yes	Yes	....	....	Thoracic	Necropsy	.....	Localized, distal to renals	3 cm. Length, 0.8 cm. diameter, secondary thrombosis	Infarct, left kidney	Proximal to coarctation
Steele [12]	1941	28*	F	W	260/180	120/100	Reduced	....	....	....	Yes	Lower thoracic	Necropsy	CVA†	Localized, adjacent to renals	0.2 cm. diameter	.....	.....
Kerr [13]	1947	....	....	.....	.....	.....	.....	....	Yes	....	....	Abdominal	.....	.....	Localized, adjacent to renals	.....	.....	.....
Wang [14]	1949	56	M	.....	160/100	.....	.....	....	....	....	....	.....	Necropsy	CHF‡	Localized, proximal to renals	.....	.....	.....
Bahnson [7]	1949	28*	F	W	230/110	Not obtained	Absent	Yes	Yes	....	No	Absent	Aortogram and operation	.....	Localized, adjacent to renals	Complete occlusion at the L-1 level	Left renal artery smaller than normal, right not seen	.....
Kondo [10]	1950	12*	F	Japanese	40/Not obtained	Not obtained	Absent	Yes	Yes	No	No	Thoracic	Necropsy	CHF‡	Diffuse, adjacent to renals	Terminal aorta constricted; aortic "valve" structure	.....	.....
Freeman [15]	1950	9*	F	.....	225/125	130/Not obtained	Absent	Yes	Yes	No	....	Thoracic	Aortogram	CVA†	Localized, adjacent to renals	Construction T-11 through L-1 level	.....	.....
Goldzieher [9]	1951	39*	F	W	180/120	300/180	.....	....	....	....	No	Abdominal	Operation	.....	Localized, adjacent to renals	.....	.....	.....
Glenn [8]	1952	9*	F	W	235/120	150/115	Reduced	Yes	....	No	No	.....	Operation	.....	Localized, proximal to renals	10.5 cm. Length	Berry aneurysm, right renal artery	.....
Fisher [5]	1952	13*	M	W	238/160	256/100	Normal	....	....	....	No	Intra-abdominal	Operation and necropsy	CVA†	Localized, adjacent to renals	2.5 cm. diameter at renals	Stenosis, both renal arteries	Proximal to coarctation
Albanese [16]	1953	12*	F	.....	210/130	Not obtained	Absent	....	Yes	....	Yes	.....	Aortogram	Encephalopathy	Diffuse, adjacent to renals	6 cm. Length, 0.5 cm. diameter; terminal aorta hypoplastic	Stenosis, both renal arteries; aneurysm, right renal	.....
Poutasse [6]	1955	15*	M	W	180/115	210/120	Normal	....	....	....	No	Absent	Aortogram	.....	Localized, adjacent to renals	.....	Stenosis, both renal arteries	.....
Martin [17]	1956	20*	M	W	190/105	130/95	Reduced	Yes	Yes	....	No	Absent	Aortogram	.....	Localized, proximal to renals	.....	.....	.....
Bunnag [18]	1957	22	F	Siamese	140/70	Not obtained	Reduced	Yes	....	Yes	No	.....	Aortogram	.....	Localized, distal to renals	4 cm. Length at L-2 to L-3 level	.....	.....
Brust	1958	9*	M	W	250/145	240/150	Normal	Yes	Yes	Yes	No	Absent	Aortogram and necropsy	CVA†	Localized, adjacent to renals	4 cm. Length; 1.3 cm. diameter	Stenosis, both renal arteries	Proximal; slight distal atherosclerosis
Brust	1958	22*	F	W	250/120	240/135	Normal	Yes	Yes	Yes	No	Absent	Aortogram and necropsy	Cerebral, aortogram complications	Localized, adjacent to renals	4 cm. Length; aortic "valve" structure	Stenosis, both renal arteries	Proximal; slight distal atherosclerosis

* Age at discovery of hypertension.
† CVA—Cerebral vascular accident.
‡ CHF—congestive heart failure.

tion; and in eight reports since 1949, including our two cases, aortography materially contributed to confirmation of the diagnosis. The potential hazard of aortography in such patients is exemplified by the fatal complication in our second patient.

Except for complaints of vague abdominal pain in a few of the patients from the literature, the clinical symptomatology afforded little help in establishing the diagnosis. The frequency of severe headache in these patients is most likely a reflection of the severity of their hypertensive disease.

In spite of their youth, seven patients suffered fatal or disabling cerebral complications from their hypertension on one or more occasions. One child had a cerebral accident at age nine and two (including our first patient) died of massive intracerebral hemorrhage at age fourteen. Two patients died of congestive heart failure, one a twelve year old child.

Surgical Considerations. Due to errors in diagnosis two patients had bilateral thoracolumbar sympathectomies [*7,8*], two underwent unilateral nephrectomy (our first patient) [*5*], and one was explored for pheochromocytoma [*9*]. In only one of the earlier patients reported was a fairly definitive surgical approach employed. In their patient, Glenn and his associates [*8*] were able to anastomose the distal end of the splenic artery to the aorta above the point of constriction, thereby reversing the flow in the splenic artery and bypassing the coarctation. Obviously such an approach would be feasible only in patients with localized constrictions well above the level of the renal arteries.

Successful homografting of both renal arteries was reported in 1956 by Poutasse et al. [*6*]. In a two-stage procedure the stenosed segments of both renal arteries were resected and replaced with arterial grafts. Following operation marked reduction of the hypertension was observed. This approach or a modification thereof would appear to afford the best prospect of surgical success in those patients with renal artery involvement.

Aortic and Renal Artery Pathology. The area of stenosis of the abdominal aorta was localized in fourteen patients and diffuse in three. In three the constriction was well above the renal arteries, while in eleven the narrowed segment began at or adjacent to the level of the renals. In three patients the constriction occurred distinctly below the renal outflow. Only one of these showed appreciable blood pressure elevation and it is possible that the hypertension in this patient may have been related to a well organized renal infarct which was found at necropsy.

Note was made of associated lesions of the kidneys and renal arteries in eight of the patients. Stenosis of both renal arteries was present in five patients and in a sixth patient a constricted renal artery was noted at operation. Renal artery aneurysm was demonstrated in two patients and renal infarction in another.

Information regarding atherosclerotic changes in the aorta proved to be incomplete. In three patients note was made that these changes were most pronounced proximal to the coarctation. Also in our two patients this proved to be true, but definite changes although less pronounced could also be detected distal to the constricted segment.

Associated Congenital Abnormalities. Additional congenital defects, some involving the vascular system were noted in six patients. Of particular interest is the curious valve-like structure noted proximal to the coarctation in our second patient and closely resembling that reported in association with abdominal coarctation by Kondo et al. [*10*]. Other abnormalities seen in the cases from the literature have included aortic valvular stenosis, anomalies of the vessels arising from the aortic arch, cerebral berry aneurysm, kyphosis, scoliosis, neurofibromatosis, hypoplasia of the uterus and congenital absence of the vagina.

SUMMARY

Clinical and pathologic findings have been reported in two young patients with severe hypertension resulting from coarctation of the abdominal aorta and stenosis of the proximal portions of the renal arteries by intimal proliferation. It appears likely from these cases and from those in the literature that the renal artery lesions are initiated by the high velocity jet produced by the coarctation, and that hypertension of the Goldblatt type may be expected as an ultimate consequence.

The presence of forceful arterial pulses and marked hypertension in the lower extremities are previously unrecognized features of the atypical clinical picture which these patients may exhibit. Although a systolic murmur and thrill over the abdomen and back may suggest the diagnosis, as in both cases reported here, visualization of the abdominal aorta and its

major branches is necessary for the planning of appropriate surgical intervention.

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Lead Poisoning and Porphyria*

JOHN T. GALAMBOS, M.D. *and* F. WILLIAM DOWDA, M.D.
Atlanta, Georgia

THE association between lead intoxication and abnormal porphyrin metabolism is well known [*1–3*]. However, only a single documented case of acute porphyria associated with lead poisoning has appeared in the literature [*4*].

Grotepass [*5*] was the first to demonstrate an increased amount of type III urinary coproporphyrin (UCP) in the urine of a patient with lead poisoning. He was unable to detect any urinary uroporphyrin (UUP) in this patient, but since then increased coproporphyrinuria has become a well recognized feature of lead poisoning and indeed may be employed as a screening procedure for the detection of lead exposure [*6*]. In the experimental animal lead produces the most marked and most prolonged coproporphyrinuria of any agent known [*7*].

The mechanism of action of lead on porphyrin metabolism is not well understood. Vannotti [*8*] suggested that lead inhibits the utilization of iron in the synthesis of heme in the erythroblast, resulting in the accumulation of porphyrin precursors and increased UCP excretion. This suggestion is supported by the demonstration of increased erythrocyte protoporphyrin and erythrocyte coproporphyrin [*9,10*]. Weatherall found that in lead poisoning there is little if any increase in fecal coproporphyrin excretion, and that the isomer present is the type I variety, as in normal persons. There is, however, an increase in the total fecal porphyrins other than coproporphyrin [*11*]. In rabbits poisoned with lead there is a marked increase of porphyrins in the bone marrow, due in part to accumulation of uroporphyrin type I and coproporphyrin type III [*10,12*]. It has been demonstrated *in vitro* that lead inhibits the synthesis of pyrrols and also of porphyrins at several points prior to the formation of protoporphyrin [*14*].

There are differences of opinion as to whether or not the symptoms of lead poisoning are related to interference with the action of the porphyrin enzymes. Vannotti [*8*] thought that there is probably no direct relationship. Spühler [*15*] suggested that lead interferes with heme synthesis, and that the porphyrins so secondarily produced are responsible for the production of symptoms. Chisolm and Harrison [*16*] found a direct relationship between the "metabolically active" lead present and the amounts of UCP excreted in children poisoned with lead, suggesting an intimate relationship between plumbism and porphyrin metabolism.

Hug [*4*] reported the first case of fatally terminating acute porphyria in association with acute lead poisoning, in a twenty-four year old man following brief exposure to lead. In this patient ascending paresthesia and anesthesia, and progressive symmetrical weakness and paralysis developed, first of the upper and then of the lower extremities. Death due to respiratory paralysis occurred fourteen days after the onset of symptoms. The blood lead concentration was 142 μg./100 gm. The urine was strongly positive for "urobilinogen." (The solubility of this pigment in organic solvents and its absorption spectrum were not determined.) The twenty-four-hour UCP excretion varied between 2.6 mg. to 8.7 mg. and the twenty-four-hour UUP excretion ranged between 2.6 mg. to 15.3 mg. The total fecal porphyrin concentration was 17.8 mg. per 100 gm.

Earlier claims that UUP is present in normal urine [*17,18*] were confirmed recently by the application of refined technics [*19*]. Previously, uroporphyrin had been demonstrated in the urine of patients with lead poisoning only occasionally and in trace amounts [*4*]. Recently [*19*], in a group of workers exposed to lead, some with symptoms of lead poisoning, the daily uroporphyrin excretion was found to be increased from the normal 13 ± 10 μg. to an average of 96.2 μg. Small amounts of porphobilinogen also were detected in the urine of these exposed workers, by the use of a method which depends on calcium acetate-acetone precipitation when the ordinary test is negative [*19*].

The symptoms of lead poisoning are similar

* From the Department of Medicine, Emory University School of Medicine, Atlanta, Georgia.

in many respects to those of acute intermittent porphyria (AIP), and the latter may be overlooked if not tested for. A case is described to stress the fact that the signs and symptoms of acute intermittent porphyria may occur for the first time in patients with acute plumbism.

METHODS

Lead was determined in blood and urine by the Bambach-Burkey modification of the Hubbard-Clifton-Whiteman method [*20*].* Urinary porphobilinogen (Pb) was tested by the method of Watson and Schwartz [*21*]. Urinary coproporphyrin (UCP) was measured according to the method of Schwartz et al. [*22*]. Urinary uroporphyrin was measured as described by Sveinsson et al. [*23*] and by With [*24*]. Erythrocyte porphyrins were measured according to the method of Schwartz and Wikoff [*25*].

CASE REPORT

L. L., a forty-four year old white man, was admitted to the University Hospital because of throbbing epigastric pain, constipation, increased weakness, anorexia and occasional tingling in his arms and hands. He consumed alcohol freely, but ate a good diet and had been in excellent health all of his life. Nine to ten weeks prior to admission he had been working as a grinder, removing lead solder from automobile bodies. He used the usual precautionary measures but noticed that at times he had flakes of lead material in his mouth, under his dentures and in his nose. Blood and urine tests for lead (four weeks prior to admission) showed a safe exposure range.

Two weeks prior to admission the patient noticed the onset of dull aching and sometimes of throbbing pain in the epigastrium, followed very closely by anorexia, weakness, constipation and the appearance of a dark reddish brown color to his urine. The blood lead was found to be 0.98 mg. per cent and the urine lead rose to 0.53 mg./L. During this interval he noticed the onset of tingling in his arms and hands.

The family history was entirely non-contributory in all respects.

The patient was a well developed man who appeared to be chronically ill. The temperature was 100°F., blood pressure 140/98 mm. Hg, respirations 20. There was generalized abdominal tenderness and two days later weakness of extensor muscles of the forearm.

Urinalysis showed many white blood cells in the sediment. The hemoglobin was 13.0 gm. per 100 cc., red blood cells 4.5 million per cu. mm. A large number of erythrocytes had basophilic stippling. The white blood cell count was 12,000 per cu. mm. with 67 per cent polymorphonuclears, 22 per cent lymphocytes, 9 per cent monocytes, 1 per cent eosinophils, and 1 per cent band forms. The serum sodium was 123.6 mEq./L.; chlorides 77.3 mEq./L.; the serum potassium and bicarbonate were essentially normal.

The roentgenogram of the abdomen, gallbladder series, skull series, intravenous pyelograms and gastrointestinal series were normal. The electrocardiogram was normal.

Large amounts of uroporphyrins were found in the urine, which also was strongly positive for porphobilinogen. The coproporphyrin excretion was 2,572.5 μg. in twenty-four hours. On three successive days the urinary lead excretion was 0.09 mg./L., 0.18 mg./L., and 0.16 mg./L., respectively. After the third day the patient was given three intravenous infusions containing calcium disodium ethylene diamine tetra-acetate (EDTA). The urinary lead excretion in the following twenty-four-hour period rose to 1.465 mg./L.

The patient had been given barbiturates and belladonna derivatives prior to his admission and these were continued for several days during the initial hospitalization. When porphobilinogen was detected in the urine these medications were discontinued. His severe psychosis markedly improved, and with correction of his electrolyte balance and treatment of his bladder infection with antibiotics the patient further improved. Following the three-day course of calcium EDTA his symptoms of abdominal pain and weakness of the extensor muscles of the forearms disappeared.

The patient was seen two months after discharge from the hospital. The urine examination was strongly positive for porphobilinogen. The twenty-four-hour UCP excretion was 1,086.8 μg. and the twenty-four-hour UUP was 657.2 μg. The erythrocyte protoporphyrin was 41.0 μg. per 100 cc. red blood cells, and the erythrocyte coproporphyrin was 1.0 μg. per 100 cc. red blood cells. For the past sixteen months the patient has felt quite well.

COMMENTS

The repeated demonstration of large amounts of porphobilinogen and uroporphyrin in the urine of a patient who has the symptoms of acute intermittent porphyria (AIP) is considered diagnostic of porphyria. The question naturally follows: What was the relationship between the entry of lead into the tissues of this patient and the development of AIP? Did this patient have latent porphyria, with lead the precipitating factor, or is the relationship between lead intoxication and the subsequent AIP a "post hoc" but not a "propter hoc" one?

If lead poisoning could cause AIP, one would expect to see many such cases in view of the relative frequency of plumbism. The fact that

* Lead determinations were performed by the Laboratory of Industrial Hygiene, Department of Health, State of Georgia. Blood and urine specimens were collected in acid-washed Pyrex glassware for lead analysis.

only a single documented case and one questionable case of AIP associated with lead poisoning have yet been reported [*4,15*] makes it seem rather unlikely that lead can cause AIP in a person with otherwise normal porphyrin metabolism.

In normal animals injury by chemical and physical agents may produce a temporary condition which has the chemical features of human porphyria [*26*]. These observations could imply that extrinsic factors alone may be responsible for porphyria in man, and that porphyria may not always reflect an inborn error of metabolism. However, the fact that porphyria is inherited as a Mendelian dominant characteristic [*27*] strongly suggests that in man extrinsic factors may precipitate the clinical syndrome only in those persons who already have the innate trait.

The liver is the major site of abnormal pyrrol metabolism in AIP [*28*]. In its effect on porphyrin metabolism lead poisoning is thought to act primarily on heme synthesis in the bone marrow. Rabbits poisoned with lead show a high concentration of porphyrins in the bone marrow and little in the liver, and excrete only minute amounts of porphobilinogen in the urine.

The effect of lead on the pyrrol metabolism in the liver may be influenced by its port of entry. A high concentration of lead can be demonstrated in the liver when lead is ingested, the usual port of entry in asymptomatic workers exposed to lead. The lead content of the liver is quite low when it enters the body through other portals [*1*].

SUMMARY

A review of the literature revealed only a single documented case of acute intermittent porphyria (AIP) associated with lead poisoning. Another case of plumbism followed by AIP is described, and the relationship between lead poisoning and porphyria is discussed.

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Portal Venous Pressure in "Pipestem" Fibrosis of the Liver Due to Schistosomiasis*

ARTHUR H. AUFSES, JR., M.D., FENTON SCHAFFNER, M.D., WILLIAM S. ROSENTHAL, M.D. *and* BERNARD E. HERMAN, M.D.

New York, New York

HEPATIC schistosomiasis is probably, from a world-wide point of view, the most frequent cause of portal hypertension. In this condition there is a considerable increase in connective tissue in the liver, but whether this form of hepatic fibrosis represents a true cirrhosis is controversial. It is also a matter of debate whether the mechanism producing portal hypertension in hepatic schistosomiasis is the same as in cirrhosis; i.e., whether the intrasinusoidal pressure is increased, as in true cirrhosis, or there is only constriction of the portal vein branches without involvement of the parenchyma. Morphologic evidence has favored the latter explanation. In the case to be presented the opportunity arose to obtain functional evidence on this point by pressure measurements. The results support the view that portal hypertension in hepatic schistosomiasis is not associated with a significant increase in intrasinusoidal pressure.

CASE REPORT

M. S. H. Case No. 97836. A twenty-two year old Puerto Rican man was admitted to The Mount Sinai Hospital because of pain in the left upper quadrant of the abdomen and weakness of seven months' duration. The pain, which originally was intermittent and knife-like, and aggravated by eating, gradually became more persistent and at the time of admission was constant. The appetite remained good, but the patient had lost 3 or 4 pounds in weight. He had never had chills or fever, nausea, diarrhea, jaundice or bleeding. Since the onset of the pain, the patient had experienced a vague feeling of weakness without syncope or vertigo. One week prior to admission a mass was noted in the left upper quadrant.

The patient had come to the United States from Puerto Rico two years before. His mother, father and ten siblings were alive and well. The history otherwise was non-contributory.

Physical examination at the time of admission was entirely within normal limits except for enlargement of the liver to 2 fingerbreadths below the right costal margin, and a firm, slightly tender spleen palpable 4 to 5 fingerbreadths below the left costal margin.

On admission the hemoglobin was 13 gm. per cent; red blood cell count, 4,720,000 per cu. mm. with 1.9 per cent reticulocytes; white blood cell count, 5,300 per cu. mm. with a normal differential count. The platelet count was 106,000 per cu. mm. The erythrocyte sedimentation rate, urine analysis, blood urea nitrogen and fasting blood sugar were within normal limits. The serum albumin was 4.2 gm. per cent, globulin 4.4 gm. per cent. The serum bilirubin and cholesterol were normal, the alkaline phosphatase was 18.2 King-Armstrong units. Four per cent bromsulfalein retention was noted in forty-five minutes. The cephalin flocculation test was 1 plus, and the serum glutamic oxalacetic transaminase was 47 units. An electrocardiogram was normal. Bone marrow examination revealed no abnormalities. The stool initially gave a 4-plus guaiac reaction but thereafter ten successive stool examinations showed no evidence of occult blood. Roentgenographic examination of the gastrointestinal tract disclosed esophageal varices. Sigmoidoscopic examination revealed hemorrhoids. A biopsy specimen of the rectal mucosa showed non-viable Schistosoma mansoni ova. A course of Fuadin® was given between January 19 and February 6, 1958. During this time evidence of liver cell damage appeared, the cephalin flocculation becoming 4 plus, and the transaminase rising to 119 units. The white blood count ranged between 5,000 and 9,000 and platelet counts between 66,000 and 140,000 per cu. mm.

Two liver biopsy specimens were obtained, and both showed essentially normal liver tissue. At esophagoscopy, extensive varices were found, beginning 28 cm. from the incisor teeth. Catheterization of

* From the Departments of Surgery, Pathology and Medicine of The Mount Sinai Hospital, New York, New York. Supported by the Research and Development Division, Office of the Surgeon General, Department of the Army under Contract No. DA-49-007-MD-790, and supported in part by Grant HTS 5206, The National Heart Institute, U. S. Public Health Service.

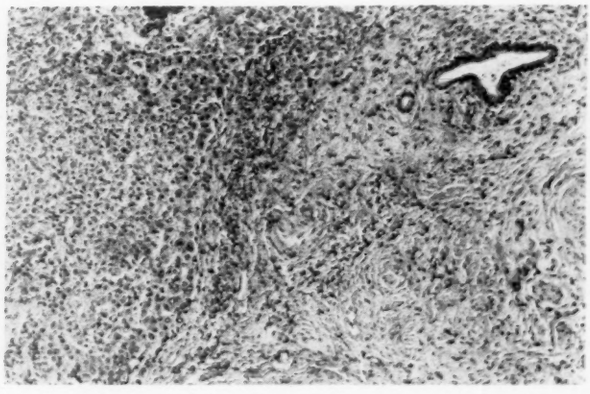


FIG. 1. Extensive portal fibrosis with obliteration of smaller branches of the portal vein. The parenchyma appears to be normal, as do the septal bile ducts. Hematoxylin and eosin, magnification × 63.

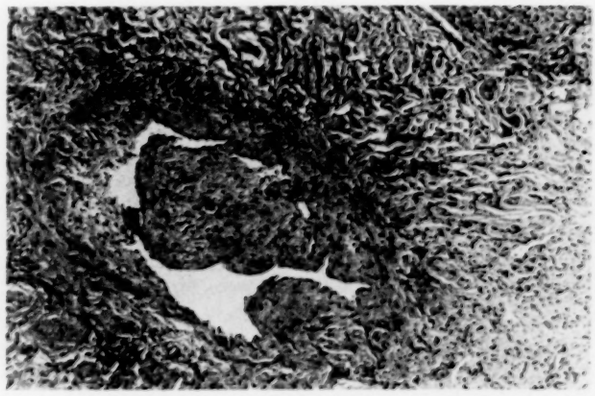


FIG. 2. An organized thrombus in a large branch of the intrahepatic portion of the portal vein, with extensive periphlebitic scarring. Hematoxylin and eosin, magnification × 120.

the hepatic vein revealed a wedge pressure of 97 mm. of water (7 mm. Hg). (Table 1.) Splenoportography was performed during which the splenic pulp pressure was recorded as 370 mm. of water. The splenic and portal veins were found to be patent. There was no filling of any collateral vessels on two attempts.

A splenorenal shunt operation was performed through a left thoracoabdominal incision in the ninth intercostal space. The lobular architecture of the liver appeared to be intact, but several broad bands of fibrous tissue traversed its surface. No nodularity was noted. The spleen was enlarged to four or five times the normal size and was firm and smooth. There was a slight increase in collateral vessels around the spleen. The mesenteric vessels were distended; the pressure in the gastroepiploic vein was 270 mm. of water. The portal vein appeared to be normal in size. The major splenic vein measured 1.5 cm. in diameter, within normal limits. Splenectomy was performed, followed by end-to-end anastomosis between the splenic vein and a renal vein branch. At the completion of the procedure, blood was seen to flow through the anastomosis and a pressure determination in a branch of the middle colic vein showed a fall of 90 to 100 mm. of water from the preshunt pressure.

The postoperative course was uneventful. Roentgenograms of the upper gastrointestinal tract taken during the convalescent period revealed a decrease in the size of the esophageal varices. Following discharge from the hospital the patient has been seen in the outpatient department and is asymptomatic, although some varices were still visible by esophagoscopy three months after surgery.

TABLE 1

MEASUREMENTS OF PORTAL PRESSURE IN A PATIENT WITH PIPESTEM FIBROSIS

Wedge hepatic vein pressure (unanesthetized)	97 mm. H_2O
Splenic pulp pressure (unanesthetized)	370 mm. H_2O
Middle colic vein pressure (anesthetized)	270 mm. H_2O

A biopsy specimen of the liver obtained at surgery showed essentially normal hepatic parenchymal cells with normal lobular architecture. The portal tracts were greatly enlarged and fibrotic. (Fig. 1.) Large portal veins were found to contain organized thrombi. some smaller branches were obliterated. (Fig. 2.) Arterial hyperplasia was also noted. The bile ducts were normal. Non-specific granulomas were seen. The picture was in keeping with the type of hepatic schistosomiasis first described by Symmers as "white clay-pipestem cirrhosis" [*1*]. The spleen showed fibrocongestive splenomegaly with foci of fibrosis containing iron and calcium.

COMMENTS

Portal hypertension from intrahepatic causes is generally associated with increased portal vein tributary pressure and with increased wedged pressure in the hepatic veins [*3–5*]; indeed, the use of wedged pressures in the estimation of portal pressure is based on the forward transmission of pressure through the sinusoids [*6*]. The chief causes of portal hypertension in cirrhosis are pressure on the hepatic vein branches by regenerative nodules and increase in hepatic artery flow [*7,8*]. Fibrosis in the portal areas *per se* has been said to be of less importance in the genesis of portal hypertension. In this case, however, no nodular regeneration was found grossly at operation or microscopically in two needle biopsy specimens and in the surgical specimen. Furthermore, no alterations of the hepatic parenchyma or small portal tracts were seen.

In 1904 Symmers described a form of hepatic fibrosis in patients infested with S. hematobium

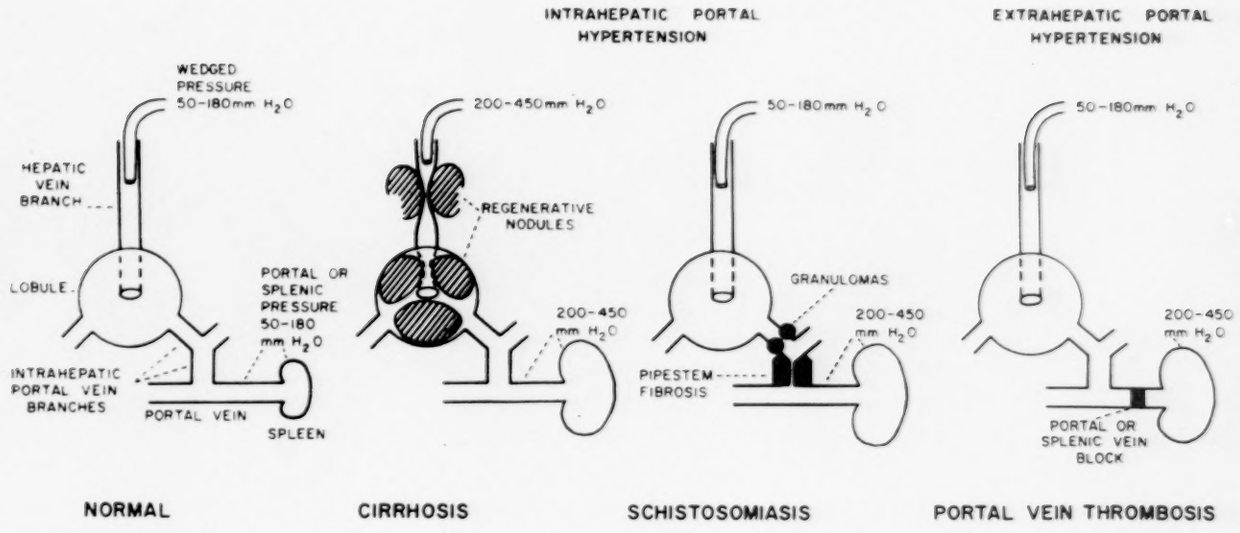


FIG. 3. Diagram of intrahepatic and extrahepatic portal hypertension showing wedged pressures and portal vein or splenic pulp pressures.

[*1*]. He compared the broad bands of fibrous tissue around the larger portal veins to the stems of white clay pipes; he also recognized that the hepatic parenchyma was normal, apart from anemia. The same lesion has been found in the presence of S. mansoni and S. japonicum [*2*]. The relation of this fibrous reaction to the portal hypertension usually found in schistosomiasis has been the subject of much controversy.

Lichtenberg is of the opinion that granulomas in the portal radicles, fibrosis in the portal fields, and intrahepatic thrombophlebitis are responsible for portal hypertension in schistosomiasis, the last factor being found only in "pipestem" cirrhosis [*9*]. Bogliolo, on the other hand, states that a granulomatous fibrotic periphlebitis develops, with new formation of a network of blood vessels around the dichotomic portal vein branches, like "a mossy sleeve" [*10*]. Involvement of the extrahepatic portal vein has been mentioned as a possible factor, but Koppisch states that this is unusual and that intrahepatic portal vein inflammation and fibrosis are caused directly by the presence of the ova [*11*] and not by toxic factors from the worms [*12,13*]; furthermore, that this intrahepatic fibrosing phlebitis or periphlebitis is responsible for the portal hypertension.

The present study indicates that the dynamics of this form of portal hypertension are similar to those found in extrahepatic portal vein disease rather than in cirrhosis, in which sinusoidal hypertension is present. (Fig. 3.) This, plus the fact that nodular regeneration and portohepatic venous anastomoses were absent, means that "pipestem cirrhosis" is not a true cirrhosis at all, but a form of hepatic fibrosis. If true cirrhosis is present it usually can be ascribed to other causes such as alcoholism [*14*].

Since esophageal varices develop at a relatively early age in many patients with schistosomiasis who have no significant impairment of hepatic function, shunt surgery should be considered early as a prophylactic measure. The prognosis and precautions are the same as in patients with obstruction of the extrahepatic portal vein rather than in those with cirrhosis [*15*]. Although antimony therapy has no effect on the portal hypertension, it should be employed prior to surgery to prevent extrasplanchnic spread of ova [*2*].

SUMMARY AND CONCLUSION

A case of portal hypertension with esophageal varices due to schistosomiasis is presented in which the wedged hepatic vein pressure was normal whereas the splenic pulp pressure and mesenteric vein pressure were high. The hepatic involvement was of the type described as "pipestem" fibrosis, an instance of extraparenchymal portal fibrosis. The resulting portal hypertension is similar in genesis to that of extrahepatic portal vein obstruction rather than to the intrasinusoidal hypertension characteristic of true cirrhosis.

Acknowledgment: Thanks are due to Dr. Ivan B. Baronofsky and to Dr. Hans Popper for their guidance and many helpful suggestions in the management of this patient and in the preparation of this paper.

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Portal Hypertension Due to Schistosomiasis Mansoni*

MARIO R. GARCIA-PALMIERI, M.D. *and* RAUL A. MARCIAL-ROJAS, M.D.

San Juan, Puerto Rico

THE predominant clinical features of a small percentage of patients suffering from schistosomiasis mansoni appear to be the result of obstructive vascular phenomena occurring in the liver or in the lungs [*1–3*].

The presence of schistosomal ova in the portal venules may result in distortion of the intrahepatic circulation, pseudotubercle formation and periportal fibrosis which when severe leads to the damming back of blood, eventuating in congestive splenomegaly, collateral venous channels (including esophageal varices) and hypersplenism. It is the purpose of this paper to present a case of portal hypertension secondary to schistosomiasis mansoni in which thirty-four episodes of severe hematemesis occurred due to bleeding esophageal and gastric varices. These gastric varices gave a radiologic picture that could be easily confused with a malignant neoplasm. The patient withstood thirty-three episodes of repeated bleeding without the development of hepatic coma.

CASE REPORT

A twenty-six year old Puerto Rican radio and television salesman was admitted to the San Juan City Hospital because of repeated episodes of hematemesis. From the age of five until the age of twelve years this patient had bathed and waded in a small stream near his home in the Island of Vieques. His dietary intake had been good, consisting of milk two to three times per day, fish two to three times per week, chicken two to three times per week and the daily use of bread, rice and beans, fruits and vegetables. A diagnosis of schistosomiasis mansoni was established by a routine fecal examination when he was twelve years old. At the age of fourteen years this patient noticed a mass in the left upper quadrant of the abdomen but he did not seek any medical attention until one year later when he had three episodes of hematemesis during a three-month period. Concurrently weakness and pallor developed. The patient was hospitalized elsewhere in November 1946 where he was found to have hepatosplenomegaly, a red blood cell count of 1,970,900 per cu. mm. and a hemoglobin of 3.6 gm. per cent. The white blood cell count was 2,050 per cu. mm. of blood with 42 per cent segmented forms, 6 per cent eosinophils, 3 per cent basophils and 49 per cent lymphocytes. The platelet count was 190,000 per cu. mm. The presence of ova in the stools confirmed the diagnosis of Manson's schistosomiasis. The patient was treated with Fuadin® and four transfusions each of 250 cc. of blood. The hemoglobin rose to 60 gm. per cent and the red cell count to 3,380,000 per cu. mm. The patient improved and was discharged.

He was readmitted to the same hospital in December, 1946 because of two additional episodes of hematemesis, and a hemoglobin of 3.5 gm. per cent. The patient was given 1,000 cc. of whole blood and was discharged in early January, 1947. During that hospitalization ascites was noted but it disappeared before the patient left the hospital.

The patient was followed in the outpatient department of the same hospital until August 1947. During that period he had four more episodes of hematemesis. From 1947 to 1957 he suffered at least twelve more episodes of bleeding, after each of which he would stay in bed for two or three days before resuming normal life. The volume of each emesis was calculated to be 250 cc. to 1,000 cc. of blood, and they were always accompanied by melena. He had never had jaundice, pain in the right upper quadrant of the abdomen, anorexia or diarrhea. There was no ingestion of alcoholic beverages or exposure to hepatotoxic drugs.

On March 18, 1957, he was admitted to our service because of an episode of severe hematemesis and melena six days previously.

The physical examination revealed a well developed, undernourished, pale white man who was well oriented and in no severe distress. The blood pressure was 100/70 mm. Hg; pulse, 82; respirations, 16 per minute; temperature, 99.4°F.; weight, 108 pounds. The conjunctivas were pale and there was no adenopathy. The lungs were clear and the heart was not enlarged. No murmurs were heard. A hard,

* From the Departments of Medicine and Pathology of the School of Medicine, the University of Puerto Rico, and the San Juan City Hospital, San Juan, Puerto Rico.



FIG. 1. Extensive esophageal varices.

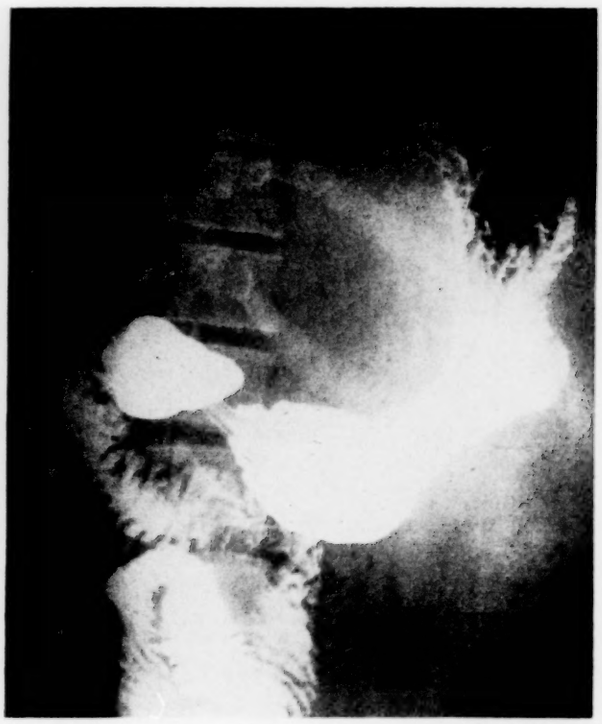


FIG. 2. Soft tissue tumefaction at the lesser curvature aspect of the cardia which represents a mass of varicosities.

non-tender spleen was felt 14 cm. below the left costal margin at the midclavicular line. The liver was enlarged 2 cm. below the right costal margin at the midclavicular line. There was visible collateral abdominal circulation. There was no evidence of spider angiomas, liver palms, gynecomastia, ascites, loss of body hair, testicular atrophy, edema of the ankles, hemorrhagic manifestations or hemorrhoids.

Hematologic studies revealed a red blood cell count of 2,680,000 per cu. mm. and a hemoglobin of 6.2 gm. per 100 cc. of blood. The mean corpuscular volume was 69 cu. μ., the mean corpuscular hemoglobin was 19 $\mu\mu$g., and the mean corpuscular hemoglobin concentration was 28 per cent. The white blood cell count was 1,850 per cu. mm. with 73 per cent neutrophils, 24 per cent lymphocytes and 3 per cent eosinophils. The platelet count was 58,000 per cu. mm. Another platelet count was 106,000 per cu. mm. The clotting time was five minutes and the bleeding time one minute and fifteen seconds. The clot retraction was complete in one hour, the prothrombin consumption test was forty seconds. The fibrin index was eight seconds with a control of six seconds. The bone marrow showed moderate depression of platelet formation and erythroid hyperplasia.

The serum proteins were 6.9 gm. per cent with an albumin of 4.3 and globulin of 3.6 gm.; the cephalin flocculation test was 3 plus in forty-eight hours; serum bilirubin, 0.54 mg. per 100 cc. in one minute and 1.08 mg. per 100 cc. in thirty minutes; thymol turbidity, 1.8 units; total cholesterol, 199 mg. per 100 cc. of serum, with 56 per cent esterification, and the serum alkaline phosphatase was 2.8 Bodansky units. The prothrombin time was 16.3 seconds, with a control of 12.4 seconds. The serum glutamic oxalacetic transaminase was 20.4 units and the serum glutamic pyruvic transaminase 21.39 units. Serological tests for syphilis were negative. The urine was normal. The blood urea nitrogen was 17 mg. per 100 cc. Serum electrophoresis revealed an albumin of 50.3 per cent; alpha-one globulin 5.65 per cent; alpha-two globulin 6.9 per cent; beta globulin 15.7 per cent; gamma globulin 21.4 per cent. The chest film was within normal limits, as was the electrocardiogram.

Esophagogram and upper gastrointestinal series (Figs. 1 and 2) showed extensive varices throughout the entire esophagus. A sharply defined soft tissue tumefaction was identified at the lesser curvature aspect of the cardia of the stomach and was interpreted as representing either a confluent mass of varicosities or a soft tissue tumor. The stomach showed extensive medial displacement by a markedly enlarged spleen, the inferior border of which was identified at the level of the iliac crest.

While in the hospital this patient had twelve distinct episodes of hematemesis which were treated by intubation with either the Sengstaken–Blakemore or Nachlas tubes, and multiple blood transfusions. The tubes were unsuccessful in halting the hematemesis on some occasions, apparently due to their inability to compress the extensive gastric varices. The patient

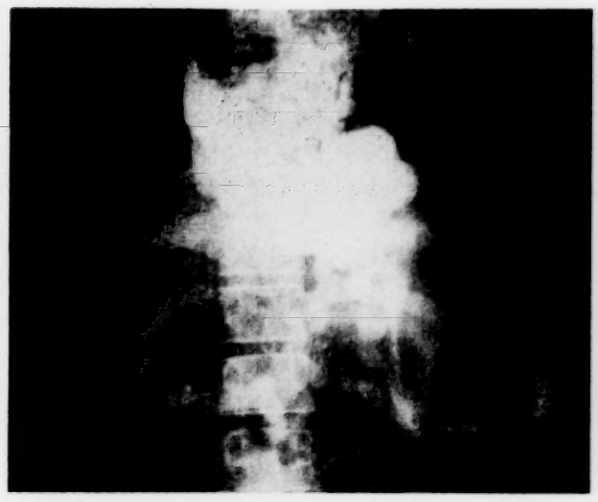


FIG. 3. Splenoportogram demonstrates large gastric and esophageal varices. The portal vein is not visualized.

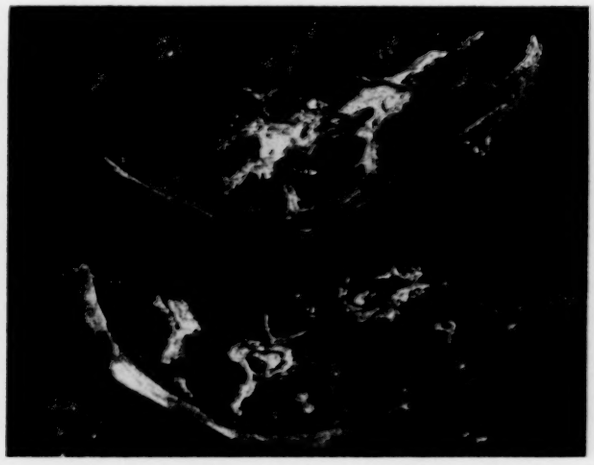


FIG. 4. Classic "pipestem" type of portal fibrosis due to schistosomiasis. The portal vein contains a thrombus.

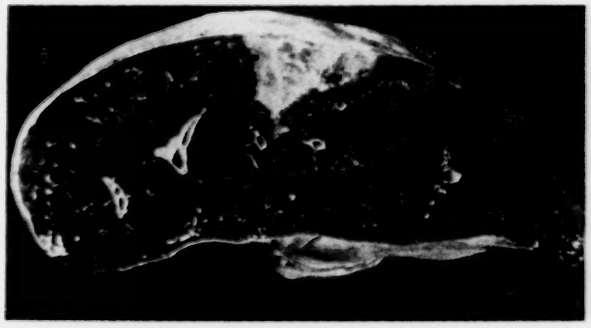


FIG. 5. Enlarged spleen with fibrosis of the pulp and an infarct. There was a small accessory spleen.

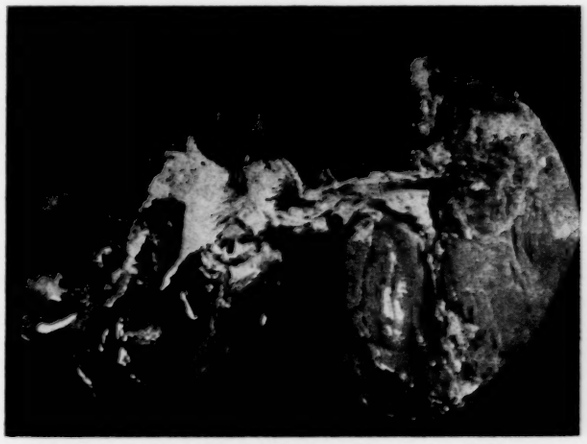


FIG. 6. Hepatomegaly and splenomegaly. The portal vein is partially occluded by thrombus. The splenic vein is markedly dilated and thickened.

was responsive and alert. The serum albumin fell to 3.0 gm. per 100 cc. on April 26, 1957, and to 2.6 gm. per 100 cc. on May 16, 1957. Multiple units of salt-free human albumin and blood transfusions were given to the patient. In spite of the administration of seventy-two units of whole blood we were not able to raise the hemoglobin to more than 7.5 gm. per cent. On April 16, 1957, ascites developed which was progressive until May 20, 1957, when a paracentesis was performed due to severe respiratory distress.

The patient's condition was considered too hazardous for any type of surgical procedure. On April 29, 1957 a splenoportogram was performed to exclude a malignant gastric lesion. It demonstrated adequate visualization of the splenic vein but failed to show the portal system. The opaque material entering the coronary vein led into a large mass of varicose veins corresponding in position to the soft tissue mass seen in the cardia of the stomach in the upper gastrointestinal series. Extensive esophageal varices also were observed. (Fig. 3.)

On June 1, 1957 the patient was somewhat drowsy and he was treated with neomycin, administered orally; a protein-free diet; glucose, administered intravenously; and repeated enemas. His condition improved. On May 8, 1957 he became somewhat confused. By the next day he was delirious, and in spite of blood transfusions, electrolytes and fluid replacement, oral neomycin and intravenous glutamic acid he died on June 11. Repeated serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase determinations had been consistently normal. An autopsy was performed three hours after death.

PATHOLOGIC FINDINGS

The body was that of a markedly emaciated young white man. The abdomen was markedly distended by fluid. The lower extremities showed prominent peripheral edema. The peritoneal cavity contained 6,000 cc. of clear strawcolored fluid. The omentum was edematous and markedly depleted of fat. The spleen projected 7 cm. below the left costal margin.

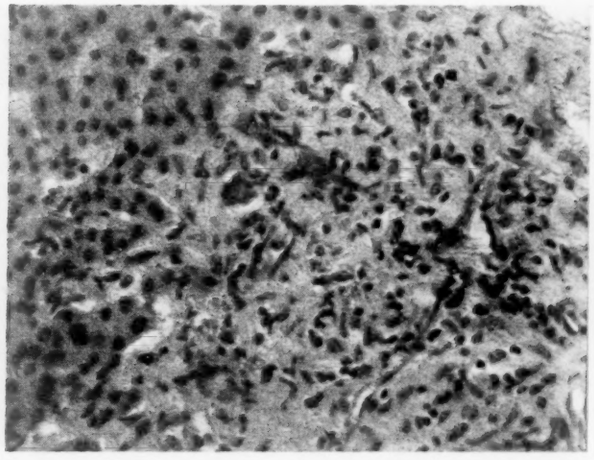


FIG. 7. The portal area is replaced by organized granulation tissue which also replaces and occludes the vein. Hematoxylin and eosin × 360.



FIG. 8. Fibroblastic activity in portal space as in Figure 7 but showing calcific residues of schistosomal ova. Hematoxylin and eosin × 360.

The right pleural cavity was obliterated by numerous fibrous adhesions, which were more prominent at the base where numerous dilated blood vessels were encountered. The heart was normal. The lungs showed marked congestion and foci of atelectasis. The liver weighed 900 gm. The surface was bosselated. On section the portal areas showed prominent fibrosis and the classic appearance of a pipe-stem type of liver. (Fig. 4.) A large thrombus was noted in the portal vein. The capsule of the left lobe was firmly adherent to the diaphragm and to the cardioesophageal junction by numerous varicosities. The spleen was markedly enlarged and weighed 1,000 gm. The capsule showed areas of hyalinization and on section the pulp was markedly fibrotic and congested. Two triangular zones of infarction were seen, the largest of which measured 5 by 3 cm. (Fig. 5.) The splenic vein was markedly dilated and measured 4 cm. in circumference. (Fig. 6.) The submucosa of the esophagus disclosed numerous varicosities along the entire length of the organ. Near the cardioesophageal junction a small ulceration of the esophageal mucosa was evident over one of the largest varicosities. The fundus of the stomach was bound to the cardioesophageal junction and to the diaphragm by innumerable markedly dilated blood vessels. At the fundus of the stomach there was a well delimited submucosal mass composed of dilated and engorged blood vessels and measuring 5 cm. in main diameter.

On microscopic examination of the liver the portal areas were found to be markedly broadened by prominent fibrosis. In most of them one failed to recognize the portal vein radicles but the artery and bile duct were always present. In most of the areas in which the portal intrahepatic veins were not seen old fibrosis was evident. In other areas organized granulation tissue was evident and replacement of the vein by granuloma could be seen. (Fig. 7.) In some of these areas old calcific residues of schistosomal ova were found. (Fig. 8.) The hepatic cells were normal except for slight compression due to congestion of the central veins. In the spleen there were two zones, one of old and the other of recent infarction. There was prominent congestive splenomegaly with fibrosis and the formation of silicosiderotic nodules. A section of the portal vein revealed a thrombus with early organization. The lumen of the vessel was not completely occluded. In the sections of the esophagus and stomach numerous dilated submucosal and subserosal blood vessels were seen. The mucosa of the esophagus was ulcerated at a point near the cardioesophageal junction. The kidneys were not remarkable except for cloudy swelling of the tubular epithelium. The lungs showed prominent congestion.

COMMENTS

Man is the primary host of Schistosoma mansoni. In endemic areas, the schistosomal cercaria penetrates the human skin or mucous membranes apparently aided by the elaboration of hyaluronidase [*4*]. The venous circulation carries the metacercaria into the lung and from there it passes to the left side of the heart eventually to reach the intrahepatic venous system for maturation. The adult flukes migrate against the portal flow to reach the mesenteric and colonic venules and, after copulation, oviposition occurs in the mucosa and submucosa of the colon and rectum. Some of these eggs are swept into the portal venous system and they lodge in the intrahepatic venous radicles. Around these ova a granulomatous process develops which occludes the lumen of the intrahepatic portal veins, destroying their walls.

The end result of this inflammatory process is the complete fibrous replacement of the veins, accompanied by prominent perivascular portal fibrosis. This produces portal hypertension which leads to the development of collateral venous channels such as gastroesophageal varices, and to splenic enlargement which may be accompanied by the syndrome of secondary hypersplenism. In some instances a contributing extrahepatic portal obstructive factor may be encountered [5]. The present case is a typical example of this condition.

Schistosomal involvement of the liver is essentially a vascular process with little clinical evidence of parenchymatous liver damage [1]. In the present case there was absence of gynecomastia, spider nevi, loss of body hair, testicular atrophy, liver palms and edema of the ankles, in association with only mild or moderate alteration in the liver function tests. The patient tolerated thirty-three episodes of hematemesis without the onset of hepatic insufficiency. The liver parenchyma at autopsy was substantially normal in appearance.

The serum transaminases are usually normal in this phase of the disease [6]. The abnormality of the cephalin cholesterol flocculation test as well as the hyperglobulinemia can be explained as a response of the reticuloendothelial system to the adult worms and ova [1]. As these patients have less alteration in the liver function tests than usually expected in cases of intrahepatic vascular obstruction, the use of splenoportography is very helpful in differentiating this group from patients with extrahepatic portal obstruction. This diagnostic procedure is recommended in all patients prior to surgery. The huge spleen, associated with neutropenia, thrombocytopenia and a hyperplastic bone marrow, points to secondary hypersplenism, which is a frequent finding in schistosomal portal hypertension.

The success of therapeutic measures for the total eradication of Schistosoma mansoni infection has thus so far fallen short of expectation [7,8]. Once bleeding from varices secondary to schistosomal portal hypertension occurs, the immediate use of the Sengstaken-Blakemore or Nachlas tube is indicated, as well as the administration of blood and replacement of fluids and electrolytes as required. The onset of hepatic coma in association to the initial episode of bleeding is not a frequent finding in schistosomal portal hypertension. If bleeding of the varices cannot be controlled with intubation, due to their gastric localization, emergency ligation as a temporary measure is imperative. Once the acute episode of bleeding is controlled the patient should be prepared for shunt surgery. We prefer end-to-side portacaval anastomosis even in the presence of hypersplenism as we believe that it is the most effective procedure [9].

The lesser degree of impairment of liver function occurring in these patients as compared to those with Laennec's cirrhosis makes them better surgical risks. This view is corroborated by the relatively low mortality in a series of more than forty patients with schistosomal portal hypertension who have undergone surgery [9].

SUMMARY

1. A patient with portal hypertension due to schistosomiasis mansoni who withstood thirty-three episodes of hematemesis is described.

2. The fundamental intrahepatic vascular alterations encountered in this disease are reemphasized. These explain the picture of marked portal hypertension accompanied by minor alterations in liver function tests and in the structure of the liver parenchyma. These differences are important in the clinical differentiation of this disease from patients with portal hypertension due to portal cirrhosis of the liver.

3. Decompressive portal surgery is tolerated better in patients with portal hypertension due to schistosomiasis than in those with portal cirrhosis, because of the lesser degree of parenchymatous hepatic damage.

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Paraplegia, Hypokalemia and Nephropathy, with Muscle Lesions of Potassium Deficiency, Associated with Thyrotoxicosis*

L. M. Sanghvi, M.R.C.P. (London), D.T.M.&H. (Eng.), K. D. Gupta, M.D., K. Banerjee, M.D. *and* K. Bose, M.B.B.S.

Jaipur, India

Several types of muscle disorder have been described in association with thyrotoxicosis, viz., thyrotoxic encephalomyopathy, chronic thyrotoxic myopathy, exophthalmic ophthalmoplegia, myasthenia gravis, periodic paralysis and Basedow's paraplegia. Of these disorders, hypokalemia has been described only in periodic paralysis in which lowering of the serum potassium level has been observed during the attacks of paralysis. The first case of periodic paralysis associated with thyrotoxicosis was reported in 1902 by Rosenfeld [*1*]. In a review of the literature Linder [*2*] in 1955 collected thirty-five cases and added four of his own. Recently Okinaka and associates [*3*] in an extensive study noted the occurrence of periodic paralysis in 119 of a total of 6,333 patients with hyperthyroidism operated on in three large hospitals in Japan. The patient with thyrotoxicosis to be described showed hypokalemia and flaccid paraplegia which was, however, not periodic in character but remained unaltered until antithyroid treatment was instituted.

CASE REPORT

A twenty-two year old housewife was admitted to the hospital on July 29, 1957, with the chief complaint of inability to move the lower limbs. Since 1951 she had had frequency of stools, numbering 4 to 6 per day, well formed and without any blood or mucus, but occasionally bowel movements were accompanied by griping; this frequency started about a month after her first delivery. The patient had since noted an increase in this frequency, and tremors of fingers on excitement. In February 1957, when her husband, employed in the armed constabulary, was posted on the Pakistan border she became very anxious and worried. Soon afterwards she noted fine tremors of the whole body and slight generalized weakness. Despite this she rapidly gained nearly 30 pounds of body weight during the next four months. Fifteen days prior to this admission severe diarrhea developed suddenly; she had 40 to 50 liquid stools per day, and vomited 3 to 4 times a day. During the next two days the tremors and the muscular weakness became so extreme that she became confined to bed. Two days later she lost consciousness. When she regained consciousness after four days, she noted complete paralysis of the lower limbs, slight weakness of the upper limbs, difficulty of swallowing, and regurgitation of fluids through the nose, and vomiting after swallowing. The stools numbered 4 to 5 a day. During the next three days she improved rapidly except for the paraplegia, and at the time of admission she could swallow without difficulty, had regained normal strength in the upper limbs, and had no vomiting. The stools numbered 4 to 5 per day. She thought she had lost all the weight which she had gained recently. During the last two weeks she was given only fruit juices and water orally.

She denied history of any past illness, and the family history was non-contributory. Obstetrical history revealed two normal deliveries in 1951 and 1956, respectively, and amenorrhea for the past four months.

Examination revealed a well developed young woman, fully conscious and with normal intelligence. There were fine tremors of the fingers and moderate exophthalmos. The thyroid gland was moderately enlarged with a nodule about 1 inch in diameter in the right lobe. The pulse rate was regular with a rate of 130 per minute and the blood pressure was 134/70 mm. Hg.

Neurologic examination revealed normal cranial nerves. The upper limbs showed normal power and tendon reflexes. The lower limbs showed complete flaccid paralysis, loss of tendon reflexes, and electrical inexcitability of the muscles. There was no tenderness, twitching or wasting of the muscles, which rather looked more bulky. There were no sensory changes.

* From the Department of Medicine, Sawai Man Singh Hospital and Medical College, Jaipur, India.

The plantar response was flexor on both sides. There was no disturbance of sphincter control. Examination of other systems disclosed no other significant finding.

Blood examination revealed a total white blood cell count of 4,800 per cu. mm. with 68 per cent neutrophils and 32 per cent lymphocytes; red blood cells 4,200,000 per cu. mm.; hemoglobin 10 gm. per 100 ml.; negative Kahn test; erythrocyte sedimentation rate, 6 mm. in the first hour (Westergren); and proteins 3.7 gm. with 2.5 gm. of albumin; cholesterol, 100 mg.; and urea, 35 mg. per 100 ml. Examination of the stool and the cerebrospinal fluid revealed no abnormality. Serum electrolytes, estimated on August 6 when the diarrhea was controlled, showed values of 3.6 mEq. per L. for potassium and 122 mEq. per L. for sodium. Urine examination revealed 1-plus proteinuria, and a maximum specific gravity of 1.015 after eighteen hours' concentration and Pitressin® test. The urinary output varied between 900 to 1,200 cc. in twenty-four hours. The basal metabolic rate was plus 45 per cent. Glucose tolerance test showed values of 92, 98, 102, 96 and 94 mg. per cent, respectively, in the fasting blood sample and half-hourly samples after glucose administration. Liver function tests were normal. The electrocardiogram showed marked S-T segment depression and flattening or inversion of T waves, changes compatible with hypopotassemia. (Fig. 1.)

The patient was treated with phenobarbitone and kaolin administered orally. The diarrhea subsided within a week. The paraplegia, the electrocardiogram and the serum potassium level, however, remained unaltered. Potassium chloride, 40 gm., was administered orally, in divided doses of 2 gm. every six hours, from August 7 to 12, without any improvement in paraplegia. The electrocardiogram showed some improvement. Use of the drug had to be discontinued as the patient again had diarrhea.

Methylthiouracil was started on August 16, in a dose of 300 mg. daily. On August 21, i.e., one month after the onset of the paraplegia, the patient noted the first sign of return of power when she could move the toes. From this date onwards there was dramatic improvement; on August 25 the patient could move the limbs and walk with support, and on August 31 she could walk unsupported. The electrocardiogram showed parallel improvement. After this initial rapid improvement further progress in the month of September was very slow. In October the patient was euthyroid with a basal metabolic rate of plus 1 per cent, a cardiac rate of 72 to 82 per minute, and absence of tremors and diarrhea. Despite this, the condition remained nearly stationary; there was still moderate weakness, the tendon reflexes were absent, the somewhat low serum potassium level persisted, varying between 3.2 and 3.7 mEq. per L., and the electrocardiogram continued to show an abnormal pattern. Administration of 100 gm. glucose intravenously and 0.5 cc. epinephrine subcutaneously during the euthyroid state did not produce worsening of the muscular power.

A subtotal thyroidectomy was performed on November 1. The postoperative course was uneventful. During the third postoperative week the patient again noted further rapid improvement of muscle power, and the electrocardiogram again showed parallel improvement. On November 22, the serum potassium and sodium reached normal values of 5.3 and 135 mEq. per L., respectively, but some muscular weakness and electrocardiographic abnormality remained. On December 19 she had her menstrual period after eight months of amenorrhea. The urinary concentration power was restored to normal by January 5, 1958. The muscle power was practically normal by the end of January. The tendon reflexes, however, remained absent until February 28, 1958 when, for the first time, the ankle jerks could be elicted sluggishly. The ankle and knee jerks and the electrocardiogram became completely normal during the first week in April.

Administration of glucose and epinephrine on April 22 failed to produce any muscular weakness. From April 24, thyroid extract was administered orally in a dose of 2 gr. per day. Severe tremors and generalized muscular weakness developed rapidly. The electrocardiogram again showed ST and T changes. On the fifth day of the administration of the drug she felt that paralysis was impending and the drug had to be discontinued.

When last examined on June 9, 1958, the patient felt perfectly well, had gained 32 pounds in weight postoperatively, the basal metabolic rate was plus 1 per cent, and the urine, serum electrolytes and the electrocardiogram showed no abnormality. The glucose tolerance test still showed a flat curve.

Pathologic reports: Kidney biopsy with Vim-Silverman needle, October 12: On microscopic examination the tissue consisted of medulla, and a relatively smaller area of cortex containing 6 glomeruli. The glomeruli showed slight thickening of Bowman's capsule. The predominent lesion was a diffuse hyaline degeneration of the epithelium of the proximal and distal convoluted tubules, with complete necrosis of some tubules. A few tubules showed granular or vacuolar degeneration. In the medulla, the collecting tubules were normal and the interstitial tissue showed considerable accumulation of edematous fluid. (Figs. 2A, 2B and 2C.)

March 12: There was considerable improvement of the structure as compared to the previous section. The glomeruli and the tubules were normal. The interstitial tissue showed slight edema, and foci of fibrobastic proliferation and accumulation of histiocytes.

Biopsy of the gastrocnemius muscle, October 16: The majority of the muscle fibers were normal. Groups of fibers showed considerable swelling, deep eosinophilic stain and complete loss of striations; most of these were hyalinized and some showed finely

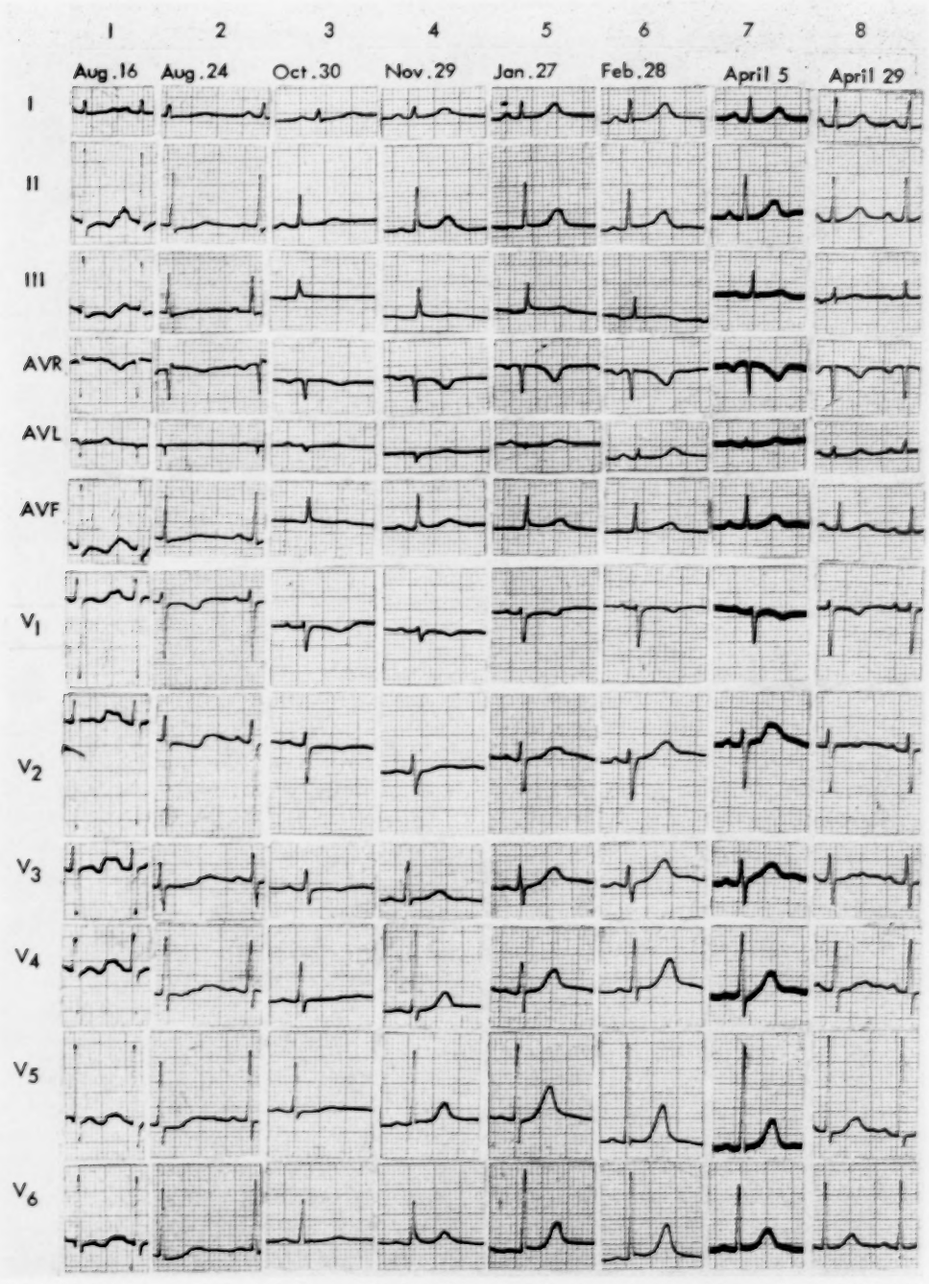
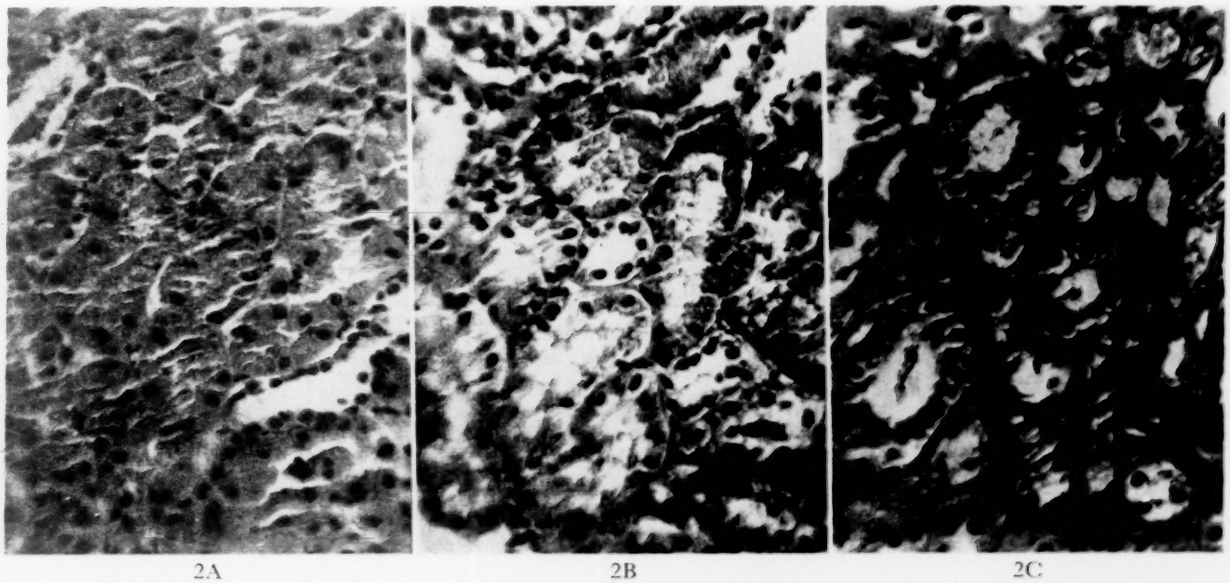


FIG. 1. Serial electrocardiograms showing: (1) before starting methylthiouracil, marked S-T segment and T changes and prominent U waves compatible with hypopotassemia; (2) eight days later, considerable improvement of pattern; (3) before operation, further improvement but still an abnormal pattern; (4) one week after restoration of serum potassium level, considerable further improvement but T waves in leads 3, aVL and V_2 are low and P wave in lead III is inverted; (5–7) gradual return to normal; (8) appearance of abnormal pattern five days after oral administration of thyroid extract.

granular appearance. There was proliferation of the sarcolemnal nuclei and fibroblasts in these areas. Some fibers were thin, rarefied and stained lightly but possessed normal striations. Few fibers showed loss of continuity. An occasional fiber showed vacuoles in its center. (Figs. 3A and 3B.)

COMMENTS

This case presents the following interesting features: (1) acute encephalopathic onset with spontaneous recovery of the bulbar palsy and coma; (2) paralysis which was limited to the

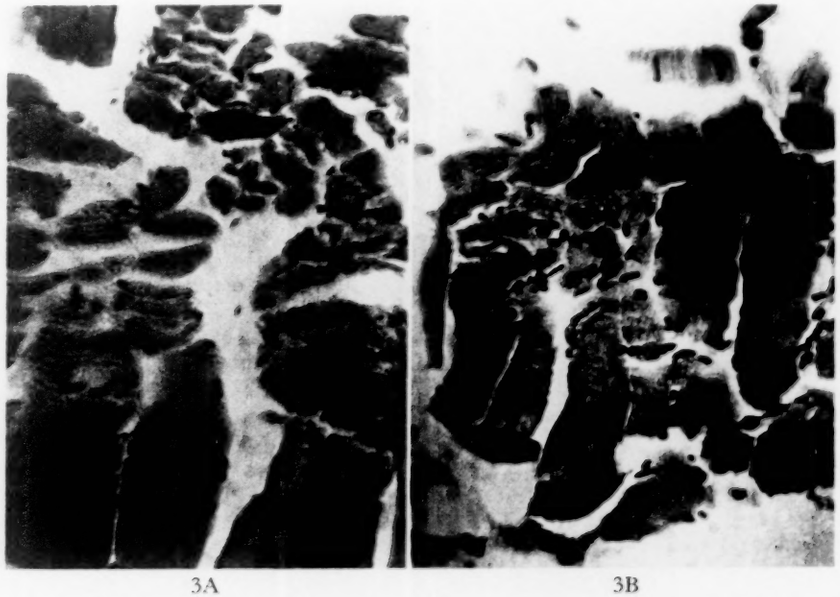


2A 2B 2C

FIG. 2. Photomicrographs of kidney. A, convoluted tubules showing swelling and hyaline degeneration. B, vacuolar degeneration and necrosis of the epithelium. C, interstitial edema in the medulla. Original magnification × 320.

lower extremities and which was not periodic in character; (3) nephropathy and muscle lesions of potassium deficiency; and (4) delayed recovery of the electrocardiogram and the muscle paralysis after restoration of the serum potassium level.

While mild symptoms of hyperthyroidism were present for nearly six years, the onset of the present illness was preceded by sudden aggravation of symptoms resulting in severe diarrhea and generalized tremors, culminating in a comatose state lasting for nearly four days. On recovery from coma there were, besides paraplegia, manifestations apparently of bulbar



3A 3B

FIG. 3. Photomicrographs of the gastrocnemius muscle. A, swollen groups of muscle fibers on the left. Original magnification × 480. B, hyaline swelling of the fibers and proliferation of sarcolemnal nuclei and fibroblasts. Original magnification × 320.

paralysis; the latter were relieved in less than three days while the paraplegia remained unaltered. The patient was not observed by us during this earlier phase of the illness but the condition is believed to be what has been referred to in the literature as acute thyrotoxic encephalomyopathy or bulbar palsy [*4–7*]. Although in earlier reports this condition was described as fatal, relief by treatment of hyperthyroidism has been reported [*4–7*]. A spontaneous recovery in our case was, therefore, a most striking feature.

The muscle disorder with complete flaccid paralysis, tendon areflexia and absence of muscular atrophy, the associated hypokalemia, and their complete cure after thyroidectomy, resemble the periodic paralysis described in thyrotoxicosis. In periodic paralysis, however, there is usually generalized muscular weakness, periodic nature of the paralysis and the hypokalemia, and spontaneous recovery which is often dramatic after administration of potassium salts. In the present case, therefore, the distinguishing features were: (1) except for the initial generalized weakness, the paralysis was limited to the lower extremities and was not recurrent but constant for a month until the antithyroid treatment was given; (2) although improvement was striking after the administration of methylthiouracil and after thyroidectomy, there was residual muscle weakness and areflexia which returned to normal several months after the operation; and (3) oral administration of potassium salts produced no improvement whatsoever. In thyrotoxicosis, Basedow's paraplegia, an obscure disorder, was reported in the earlier medical literature [*8*]. There has, however, been no mention of hypokalemia in this disorder and our case appears to be the first instance of paraplegia associated with hypokalemia.

The hypokalemia appeared to be related to the influence of excessive thyroid hormone secretion and not to the short episode of acute diarrhea preceding the present illness because of the fact that it persisted preoperatively despite control of diarrhea for nearly two and a half months, and restoration of a completely euthyroid state for more than one month. The serum potassium level became normal only after thyroidectomy. The electrocardiographic changes appeared to be severe as compared with the serum potassium level, which was never less than 3.2 mEq. per L. The electrocardiogram and the muscle disorder improved after administration of methylthiouracil and after thyroidectomy, and yet became normal several months after the serum potassium level was restored. It was thus seen that the electrocardiogram and the muscle disorder took a parallel course. Neither of them, however, showed any striking relation to the serum potassium level. This and the delayed recovery of the electrocardiogram are in sharp contrast to what has been observed in familial periodic paralysis [*9,10*]. The delayed recovery of the electrocardiogram suggests that the intracellular rather than the extracellular potassium is of primary significance in the etiology of the electrocardiographic changes [*10–12*].

Functional and structural changes in the kidneys have been described in patients with potassium deficiency due to chronic diarrhea [*13–15*] and primary aldosteronism [*16*], and nephropathy of potassium depletion has been considered a distinct clinical and pathologic entity [*15*]. Such a nephropathy has so far not been reported in thyrotoxic paralysis. Its presence in our case was suggested by the hyposthenuria, mild proteinuria and loss of ability to concentrate urine. Kidney biopsy revealed morphologic lesions. That the changes were due to potassium deficiency was indicated by the fact that the urine became normal soon after the serum potassium level became normal, and a second kidney biopsy performed four months after thyroidectomy showed considerable regression of the changes. The muscle lesion, with swollen hyalinized groups of muscle fibers and proliferation of sarcolemmal nuclei, is similar to that described by Tyler and associates [*17*] in periodic paralysis. Such muscle changes occur in periodic paralysis of unusual intensity or prolonged duration. In this case the kidney and the muscle lesions can be explained because of the constant nature of the paralysis and the hypokalemia. The vacuolar type of degeneration described as the most characteristic lesion of potassium deficiency [*13–16*] was, however, insignificant in our case both in the kidney and in the muscle. This may be due to the fact that the biopsy specimens were obtained after treatment with methylthiouracil.

The association of hypokalemia and muscle paralysis has been described in periodic paralysis, the familial or the sporadic type, associated with thyrotoxicosis, and in primary aldosteronism. There is evidence that the attacks of paralysis are related to carbohydrate metab-

olism. The exact relationship between the hypokalemia and the paralysis is not yet established. Occurrence of a shift of potassium into the muscle and marked increase of the intracellular to extracellular concentration ratio of this ion has been reported during attacks of periodic paralysis [*18–20*]. Conn and associates [*21*] recently noted that the attacks were preceded by sodium retention and a sharp rise of urinary aldosterone, and that recovery from the attack was associated with massive sodium diuresis. They consider sodium retention to be the primary factor which sets into motion the chain of events in an episode of paralysis. Van Buchem [*10*], in a case of primary aldosteronism, observed low potassium and high sodium in muscle without paralysis, indicating that sodium retention in the muscle cell by itself is not the essential abnormality. The sum of the intracellular cations may be the critical factor [*10,21*].

The exact mechanism whereby the thyroid hormone influences the potassium metabolism and causes paralysis is also not clearly understood. Increased severity of paralytic attacks with development of hyperthyroidism in familial periodic paralysis [*22*], recurrence of attacks with relapse of thyrotoxicosis in patients treated [*23*], aggravation of paralysis by thyroid administration [*24*], and occurrence of paralysis even during a completely euthyroid state after treatment with antithyroid drugs [*25*] have been variously observed. McEachern [*26*] noted the high frequency of hyperthyroidism and goiter in the series of cases of periodic paralysis reported by Shinosaki and by Tsuji. Pedersen [*27*], however, examined serum potassium levels pre- and postoperatively in cases of thyrotoxicosis without finding abnormal values. It has been suggested that hyperthyroidism brings out a latent tendency toward periodic paralysis in the affected persons [*22*].

In our case the serum potassium level had no definite relation to the muscle disorder. Administration of glucose and adrenaline, preoperatively when the patient was euthyroid, and postoperatively when the patient was completely normal, produced no deterioration in the muscle power, implying little relationship between carbohydrate metabolism and paralysis [*17*]. Administration of thyroid extract postoperatively, however, caused extreme muscular weakness and a state of impending paralysis associated with electrocardiographic changes. This is in agreement with the earlier observations of other investigators [*22–24*] and suggests that there was some inherent defect in the patient.

It is therefore believed that in the present case there was some inherent defect; that hyperactivity of the thyroid gland produced an exacerbation of this defect, resulting in paralysis and hypokalemia; that this hormonal influence was continuous, unlike the intermittent nature reported in periodic paralysis associated with thyrotoxicosis; that some influence persisted despite restoration of the euthyroid state after administration of methylthiouracil; and that this influence was completely removed only after thyroidectomy.

The question arises as to what this inherent defect might be. Conn and associates [*21*] suggested that in familial periodic paralysis there is intermittent aldosteronism and that the stimulus for the excessive aldosterone secretion is apparently extra-adrenal in origin. In our case, owing to lack of facilities, aldosterone determination could not be carried out. It is conceivable that a similar mechanism exists in paralysis associated with thyrotoxicosis. In this condition, however, the paralysis has always been relieved or cured by treatment of hyperthyroidism. The defect may therefore be an abnormal sensitivity of the extra-adrenal source to the abnormal thyroid hormone. The curious rapid gain of body weight in our case despite aggravation of the thyrotoxic manifestations just prior to the present illness suggested the possibility of some other endocrine influence. As suggested by Shinosaki [*24*] there may be a polyglandular disturbance of the glands of internal secretion.

SUMMARY

1. A case of paraplegia and hypokalemia associated with thyrotoxicosis is reported.

2. The unusual features were: (1) acute encephalopathic onset; (2) paralysis limited to the lower extremities and of a non-periodic type; (3) nephropathy and muscle lesions of potassium deficiency; and (4) delayed recovery of the electrocardiogram and the muscle disorder after restoration of the serum potassium level.

3. With restoration of the euthyroid state after antithyroid therapy the muscle disorder and the electrocardiographic changes of hypokalemia improved; they became completely normal several months after thyroidectomy. They

took a parallel course. Neither of them, however, showed any definite relation to the serum potassium level.

4. Administration of thyroid extract, postoperatively, after complete recovery of the illness, produced extreme muscular weakness associated with electrocardiographic abnormalities. It is suggested that there was an inherent defect in this patient, probably of an endocrine nature, which became manifest with the development of thyrotoxicosis.

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Simultaneous Hyperthyroidism and Hyperparathyroidism*

BOY FRAME, M.D. *and* ROBERT H. DURHAM, M.D.
Detroit, Michigan

THE simultaneous occurrence of hyperthyroidism and hyperparathyroidism has been confirmed by adequate clinical data and by operation in three reported instances [*1–3*]. In six other reported cases sufficient metabolic and histologic data are lacking to establish proof for the concurrent presence of the two disease entities [*4–9*]. In addition, Chapman and Maloof mention two additional cases, but give no clinical information [*10*].

Certain clinical features of the two diseases, particularly their effects on calcium metabolism and bone, are quite similar and may lead to confusion in diagnosis. The purpose of this paper is to report what is believed to be the fourth proved case of simultaneous hyperthyroidism and hyperparathyroidism. The common clinical features as well as the aids in differential diagnosis will be discussed.

CASE REPORT

A. B. (No. 91 21 21), a sixty-three year old farmer, was referred to the Henry Ford Hospital by Dr. William L. Martin for evaluation of weakness and loss of weight. The patient had a large nodular goiter which had been present for fifteen years without change in size. Three years before the present admission the patient was admitted to another hospital because of recurrent epigastric pain, hematemesis and melena. A large gastric ulcer of the lesser curvature, detected by roentgenograms, subsequently healed with medical management. An asymptomatic right kidney stone was also noted at this time on roentgenograms of the abdomen.

Six months before admission there was a recurrence of the gastric ulcer, which again healed with medical treatment. At this time, however, the patient began having new symptoms which consisted of increasing nervousness, tremor of the outstretched hands, and marked weakness. A 40-pound weight loss occurred over a five-month period and an increased fluid intake and urine volume was noted. On admission to this hospital the patient appeared to be pale, emaciated and seriously ill. The blood pressure was 120/60 mm. Hg, and the pulse rate 120. A definite stare and lid lag were present. There was a large, soft multinodular goiter. A coarse tremor of the outstretched hands, almost suggesting a parkinsonian tremor, was a constant feature. There was no bone tenderness or band keratitis. The admitting diagnosis was toxic nodular goiter. With past evidence of peptic ulcer, kidney stone and polyuria, the presence of hyperparathyroidism was also strongly suspected.

The initial hemoglobin was 8.5 gm. per 100 ml.; the white cell count and differential were within normal limits. The specific gravity of the urine was 1.005; the reaction for sugar and albumin was within normal limits; the sediment contained a rare white cell. While receiving a calcium diet of 150 mg., the patient excreted 302 mg. of calcium in a twenty-four-hour urinary volume of 2,650 ml. The serum nonprotein nitrogen was 58 mg. per cent, creatinine 1.9 mg. per cent, calcium 13.6 and 13.4 mg. per cent, inorganic phosphorus 3.8 and 3.4 mg. per cent, and the alkaline phosphatase 5 and 3.6 Bodansky units. The basal metabolic rate was plus 25 per cent. The protein-bound iodine in the serum was 17.4 μg. per 100 ml. Review of gastrointestinal roentgenograms taken three years and six months respectively before admission to this hospital revealed a gastric ulcer of the lesser curvature with complete healing after medical treatment had been instituted. Two subsequent upper gastrointestinal roentgenograms failed to show evidence of recurrence. In the planigrams of the kidneys a calculus was demonstrated in the lower pole of the right kidney. Demineralization and a coarse trabecular pattern were noted in the x-ray films of the hands and skull, and small cystic changes in several of the terminal phalanges. Bone biopsy performed and studied histologically by Dr. H. C. Frost was interpreted to show extensive scalloping of Howship's lacunae in the undecalcified sections, compatible with increased bone reabsorption. (Fig. 1.)

The patient was treated with 100 mg. of Tapazole® and 15 drops of saturated solution of potassium iodide daily for the next five weeks. Marked improvement in the thyrotoxicosis became apparent. The pulse rate fell to 80, the lid lag and tremor subsided, and the

* From the Department of General Medicine, Henry Ford Hospital, Detroit, Michigan.

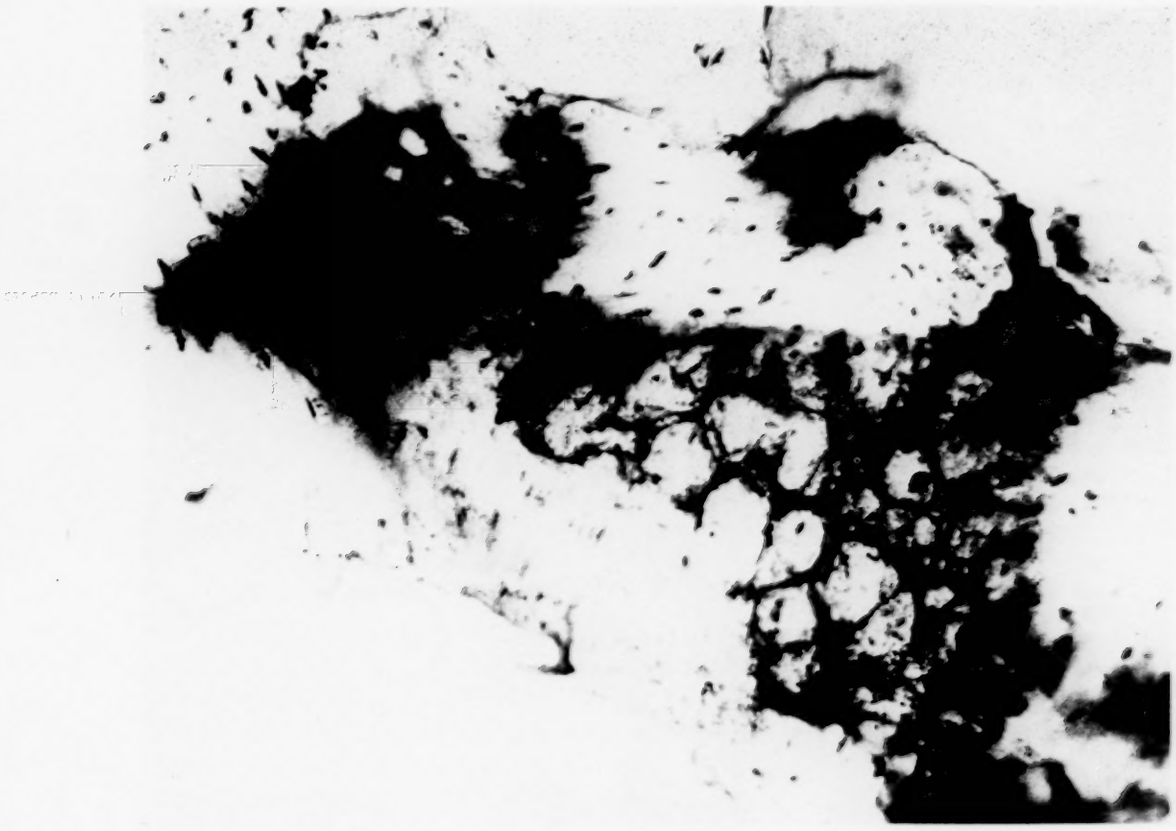


FIG. 1. Photomicrograph of fresh, undecalcified bone section from ilium, showing scalloping of Howship's lacunae (center), indicating marked bone reabsorption.

goiter regressed in size. Despite these signs of improvement the patient began to complain of anorexia, vague abdominal discomfort and marked weakness. The serum calcium increased to 14 mg. per 100 ml., and the serum inorganic phosphorus fell to 2.2 mg. per 100 ml. The tubular reabsorption of phosphorus, when the serum creatinine was 1.9 mg. per 100 ml., was 62.4 per cent.

The decisive clinical and biochemical evidence of hyperparathyroidism led to surgical exploration six weeks after admission. A parathyroid adenoma weighing 2 gm., embedded in a multinodular goiter, was removed (Figs. 2 and 3); three normal parathyroid glands were also identified. The large hyperplastic multinodular goiter weighing 325 gm. also was removed. Four days after operation, the serum calcium fell to 9.4 mg. per 100 ml. where it stabilized. The serum inorganic phosphorus remained between 2.6 and 3 mg. per 100 ml. There was marked clinical improvement with an increase in appetite, strength and weight. The calcium excretion in a twenty-four-hour urine sample decreased to 61 mg.

COMMENTS

The clinical findings of lid lag, stare, goiter, tremor and tachycardia left little doubt regarding the diagnosis of hyperthyroidism. A basal metabolic rate of plus 25 per cent and a protein-bound iodine level of 17.2 μg. per 100 ml. were confirmatory. The history of kidney stone and polydipsia suggested hypercalcemia, while the history of peptic ulcer with hypercalcemia raised the question of long-standing hyperparathyroidism. There appears to be an increased incidence of peptic ulcer in association with hyperparathyroidism [*11*]. Hypercalcemia and excessive calciuria, as observed here, can occur in hyperthyroid as well as in hyperparathyroid patients and these findings were not helpful in proving the coexistence of the two diseases. The initial serum phosphorus was normal, but in the presence of renal insufficiency the hypophosphatemia of hyperparathyroidism was believed possibly to be masked. Bone demineralization and the increased trabecular pattern seen in the roentgenograms were compatible with either diagnosis. The normal serum alkaline phosphatase was somewhat surprising in view of the moderate bone involvement. The serum alkaline phosphatase has been reported slightly increased



FIG. 2. Photograph of cut surface of parathyroid adenoma embedded in hyperplastic multinodular goiter.

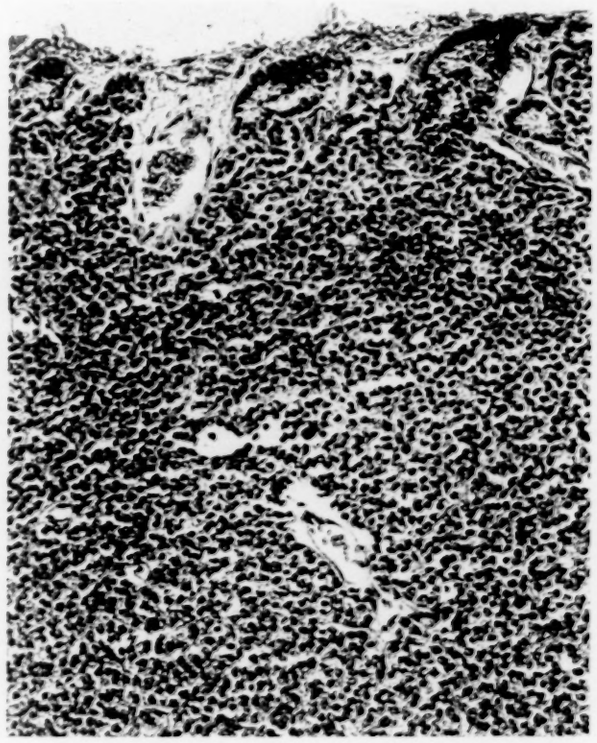


FIG. 3. Microscopic section of parathyroid adenoma, showing cords and groups of cells. The cell cytoplasm was finely granular and faintly eosinophilic.

in hyperthyroidism with bone involvement [*12*], but a distinctly high level would have been more compatible with hyperparathyroidism.

In Table 1 are listed the pertinent clinical features of four proved cases of simultaneous hyperthyroidism and hyperparathyroidism reported in the literature, including the present one. In these patients a parathyroid adenoma rather than diffuse parathyroid hyperplasia was the cause of the hyperparathyroidism. In three patients, evidence suggested that the hyperparathyroidism preceded the hyperthyroidism. In the fourth case, that of Koenig et al. [*3*], a previous history of peptic ulcer was the only clue that the hyperparathyroidism may have antedated the hyperthyroidism. In none of the cases reported was there evidence to suggest additional functioning adenomas of the pituitary, the islet cells of the pancreas, or the adrenals.

In most instances, hyperthyroidism and hyperparathyroidism present separate clinical pictures and there should be no difficulty in differentiating the two diseases. There are, however, a number of instances in the literature in which hyperthyroidism simulated hyperparathyroidism [*3,14*]. This is especially true when the elevated metabolism of hyperthyroidism is masked and symptoms of hypercalcemia and bony demineralization are the presenting complains. In most such cases the disturbed calcium metabolism returned to normal after the hyperthyroidism was adequately treated. If the hypercalcemia and hypercalciuria persisted after adequate treatment of the hyperthyroidism, the additional diagnosis of hyperparathyroidism was entertained.

Except for the signs of hypermetabolism, hyperparathyroidism may have many features in common with hyperthyroidism. The serum calcium may be markedly elevated in both diseases. A serum calcium of 19.9 mg. per 100 ml. was reported in the second case of hyperthyroidism reported by Rose and Boles [*13*]. The gastrointestinal complaints that are frequently a prominent feature in hyperparathyroidism may be related to the hypercalcemia. In the occasional case of hyperthyroidism in which there is loss of appetite and nausea rather than the usual increased appetite, hypercalcemia may also be the underlying cause. A depressed serum inorganic phosphorus is more characteristic of hyperparathyroidism but in the presence of renal insufficiency the serum inorganic phosphorus may be elevated in both conditions. The alkaline phosphatase may be slightly elevated when the skeleton is involved in hyperthyroidism, but it is usually much higher in hyperparathyroidism. It was surprisingly low in the case under discussion.

TABLE 1

DETAILS OF PROVED CASES OF SIMULTANEOUS HYPERTHYROIDISM AND HYPERPARATHYROIDISM

Author	Age (yr.)	Sex	Basal Metabolic Rate (Protein-Bound Iodine)	Serum			Urine Calcium (mg./24 hr.)	Kidney Stones	Roentgenograms	Histology	Comments
				Calcium (mg./100 ml.)	Phosphorus (mg./100 ml.)	Alkaline Phosphatase (units/100 ml.)					
Noble and Borg [1] (1932)	33	F	+38	18	2.4 3.6	.....	980	...	Bone demineralization, bone cysts	Parathyroid adenoma, clear cell type	Hyperparathyroidism preceded hyperthyroidism
Miller and Evans [2] (1942)	51	F	+29	17.2	2.5	3.2 (Bodansky)	...	Yes	Bony thorax normal	Hyperplastic thyroid, parathyroid adenoma	Hyperparathyroidism preceded hyperthyroidism
Koenig et al. [3] (1957)	60	F	+4 (12.6)	11.1	3	15.9 (King-Armstrong)	335	...	Normal	Hyperplastic thyroid, parathyroid adenoma	History of peptic ulcer before onset of hyperthyroidism
Present report	63	M	+25 (17.2)	13.6	3.8 2.2	5 and 3.6 (Bodansky)	302	Yes	Bone demineralized, with increased trabeculation	Multinodular hyperplastic thyroid, parathyroid adenoma	History of peptic ulcer; hyperparathyroidism preceded hyperthyroidism

Evidence of renal impairment possibly related to the hypercalcemia may be found in both of these diseases. This may be manifested as polyuria and decreased concentrating ability as well as severe azotemia and moderate anemia. The hypercalciuria may initially be marked in both entities but not infrequently it decreases as renal impairment progresses. Nephrocalcinosis and nephrolithiasis are well known features of hyperparathyroidism, but they also occur in hyperthyroidism when there is accompanying hypercalcemia [*3,14*]. The renal tubular reabsorption of phosphorus when significantly depressed would favor the diagnosis of hyperparathyroidism. However, recent studies have demonstrated that in dogs the administration of triiodothyronine also is followed by a reduced renal tubular reabsorption of phosphorus [*15*]. To our knowledge the renal tubular transport of phosphorus has not been evaluated in clinical hyperthyroidism. The test loses its value when there is renal insufficiency. In the case under discussion, the elevated serum creatinine of 1.9 mg. per 100 ml. at the time of the phosphorus reabsorption test partly invalidates the low result of 62 per cent. Nevertheless, it was given some significance because of its particularly low value.

Excessive destruction of bone may occur in both diseases, with resulting marked bony demineralization. Bone cysts, absence of lamina dura and phalangeal reabsorption are more specific for hyperparathyroidism. Osteitis fibrosa has been well accepted as the pathologic bone picture in hyperparathyroidism. Only recently, however, has it been realized that very similar bone changes may be present in hyperthyroidism. Follis [*16*] found histologic evidence of osteitis fibrosa in each of twenty patients studied. In six of the patients there was additional evidence of osteomalacia; in four patients the histological features of osteoporosis were also present. Further evidence of osteitis fibrosa in hyperthyroidism was presented by Krane and associates [*12*]. Their studies with radioactive calcium and isotopic dilution technics demonstrated increased rates of bone formation and destruction.

SUMMARY

A case of hyperthyroidism and hyperparathyroidism occurring simultaneously is reported. The presence of a kidney stone and peptic ulcer, present before the onset of symptoms of hypermetabolism, suggests that the hyperparathyroidism preceded the hyperthyroidism.

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Fabry's Disease (Angiokeratoma Corporis Diffusum Universale)*

An Unusual Syndrome with Multisystem Involvement and Unique Skin Manifestations

CAPT. WALTER J. KARR, JR., M.C., USA
Fort Sam Houston, Texas

BECAUSE of the paucity of cases, bizarre manifestations, multisystem involvement, possible confusion with common diseases and ease with which Fabry's disease may be diagnosed, this case is reported.

The term angiokeratoma refers to maroon, blue-black or black, flat or slightly elevated vascular lesions which measure a few millimeters in diameter. Microscopically they are dilated vascular channels which may or may not be associated with hyperkeratosis. The term first appeared in the writings of Mibelli in 1889 in reference to small vascular anomalies over the dorsum of the fingers and hands associated with exposure to cold. This condition bears the name Angiokeratoma of Mibelli.

A similar condition of angiokeratomas distributed over the scrotum in elderly men was described by Fordyce in 1896 and the condition bears his name. While these two forms of angiokeratoma are dermatological entities, the angiokeratoma described by Fabry in 1898 is the cutaneous manifestation of a systemic disease. (Fig. 1.)

Fabry [*1*] described a thirteen year old boy with slight periorbital edema and angiokeratomas scattered over the trunk. He referred to these lesions as "purpura haemorrhagica nodularis" and in a later publication designated the condition Angiokeratoma corporis diffusum universale. The follow-up article [*2*] on the original case, which appeared seventeen years later, reported that respiratory symptoms, albuminuria and an increase in the number of nodules had developed in the boy. From these observations Fabry suggested the systemic nature of the disease. However, prior to this others [*3,4*] had published data indicating their suspicion of the systemic nature of the disease.

Between the original case description and 1955, fewer than twenty-five documented cases were recorded in the world literature. Fessas, Wintrobe and Cartwright [*5*] published the first American case in 1955 and compiled an excellent review of pre-existing cases. They delineated the syndrome and discussed the possible pathogenesis. A few incomplete but probable cases were not included because of lack of systemic manifestations or biopsy confirmation. One of these patients [*6*] presented with skin lesions of the arms and penis, and bronchial asthma; he also had two brothers with similar skin lesions.

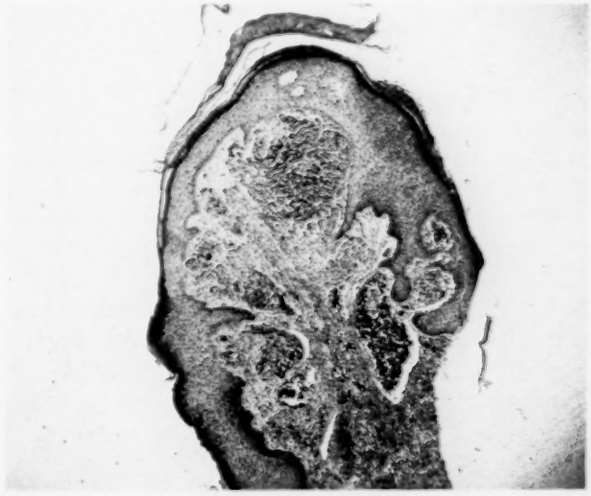


FIG. 1. This elevated skin lesion removed from the thigh demonstrates dilated vascular channels and slightly hyperkeratotic corneum.

* From the Department of Medicine, Brooke Army Hospital, Brooke Army Medical Center, Fort Sam Houston, Texas.

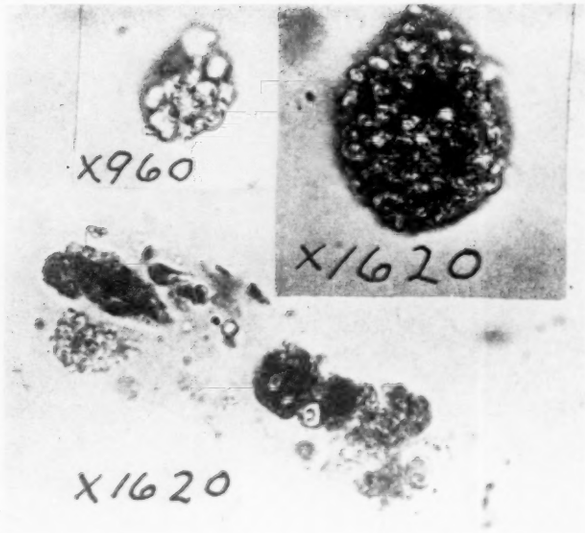


FIG. 2. Photomicrograph of composite of urine sediment demonstrating doubly refractile bodies in macrophage cells (upper field) and as an inclusion (lower field).

Another [7] was a nineteen year old boy with exertional dyspnea, edema of the hands and feet, and typical skin lesions.

Following the article by Fessas et al. [5] another American case [8] was published in 1955, and the author later published [9] the histochemical and polariscopic findings in the skin. In 1956 a twenty-three year old man with acroparesthesia and skin lesions was described [10], and in 1957 a twenty-seven year old man with skin manifestations and subjective complaints of cold hands [11]. Cunningham and Krauel [12] presented a thirty-four year old man followed up since the age of twenty-five. This man's course was characterized by intermittent ankle edema, "rheumatoid" pains, paresthesias of the extremities, occult fever as high as 106°F., and emotional lability.

The disease becomes manifest early in life by the appearance of skin lesions, followed by cardiovascular, renal and pulmonary manifestations. Swelling of the ankles and periorbital tissue, abnormalities of sweating, paresthesias, obscure fever, intolerance to cold and heat, vasomotor changes and rheumatoid pains are frequent. Asymptomatic eye changes are present and gastrointestinal symptoms have been reported. Anemia is frequent and its pathogenesis remains obscure. Considering the number of cases reported with typical skin lesions and sparse systemic manifestations, one may assume that the condition is compatible with long life. Reported deaths have occurred in middle adult life and were related to the cardiovascular renal system in three patients and to the gastrointestinal system in one.

Four patients have been examined postmortem. Ruiter, who has been interested in the disease for years and who has written extensively concerning it [13–16] presented the findings in the fourth autopsied patient, [17] who died shortly after being admitted to the hospital for gastroenteritis. This patient was one of three brothers afflicted with the disease. One brother had died in uremia, and his postmortem findings together with an unrelated case were reported in 1947 [18]. The third autopsied case was published in 1950 [19]. It was from the third autopsied case that Kuhnau analyzed the heart and found it to contain ten times the normal amount of diaminophosphatides. The abnormal substance resembled sphingomyelin but differed from it in solubility. Since that time the disease has been regarded as an abnormality of lipoid metabolism analogous to the storage diseases [19–24].

Ruiter's microscopic technic [17] in examining the last autopsied case utilized frozen sections placed in 5 per cent formalin and examined with polarized light. Fixed specimens were prepared by keeping formalin-fixed tissue in 3 per cent potassium bichromate solution for one week, with a change in the bath every three days. The tissue was then imbedded in paraffin and stained with Sudan black and fresh scarlet red. Polarized light was used to demonstrate the lipoid substance.

The vascular system is the major site of pathological change. The smooth muscle of the media of the vessels, especially the medium-sized renal arteries, contains optically empty vacuoles when stained with hematoxylin and eosin, whereas with Sudan red birefringent material is seen. In many areas the doubly refractile bodies appear to be filled with aggregates of small granules. Vacuolization has been noted in the epithelial cells of Henle's loop and Bowman's capsule. Blood vessels of the skin, gastrointestinal tract and visceral organs are involved. A peculiar foamy, fat-laden macrophage has been found in the bone marrow [5] and a similar cell has been demonstrated in the urine [5,9]. In the urine this cell contains doubly refractile bodies which have typical Maltese cross configurations by polarized light, and a similar substance has been demonstrated in inclusion casts. (Fig. 2.)

Skin lesions show vascular spaces which are dilated and filled with blood. With proper staining technic, such as outlined by Ruiter [*17*], the doubly refractile material can be seen in the media of the vessels including arterioles, capillaries, venules and veins. Pittelkow [*9*] has shown vacuolization of the erector pilorum muscles, and a paucity of sebaceous and sweat glands has been noted [*12*]. Scriba and later Ruiter [*17*] have demonstrated vacuolization and nuclear changes in the autonomic nervous system.

In the fourth autopsied case the smooth musculature of the intestinal tract appeared smudgy. Reticuloendothelial cells in the adrenals, lymph nodes, spleen and liver have been found to contain the lipoid material. Vacuolization of the bronchiolar epithelium has been seen. Cardiac hypertrophy, right-sided in one patient, was demonstrated in the first three autopsied cases and these patients were hypertensive during life.

An analysis of smooth, striated and cardiac muscle revealed an increased amount of tissue glycogen [*22*]. The nature of the lipoidal substance is obscure and attempts to isolate it from heart and lungs [*17*] have resulted in the production of an amorphous wax-like substance. No consistent abnormality of blood chemistry or lipoid metabolism has been demonstrated to date.

The etiology of the condition has not been defined. It has been reported only in males and frequently in siblings. Its occurrence in half-brothers from the same mother has been recorded [*25*]. Our patient has a father and a brother with similar skin lesions and this would seem to indicate a non-sex-linked hereditary defect. No cases have been reported among Negroes.

No satisfactory treatment has been reported. Estrogen therapy has been attempted [*12*] without results, and menadione administered with equivocal results.

The present case demonstrated most of the signs and symptoms which have been alluded to in the literature, with the notable exception of gross neurological defects and splenomegaly [*25*]. Familiarity with the physical findings and urinary characteristics usually will permit diagnosis prior to special biopsy procedures.

CASE REPORT

A thirty-three year old Latin American man entered Brooke Army Hospital in May 1958 because of fever and aching in the shoulders, elbows, knees and ankles of five days' duration. All joints had been simultaneously involved. Objective changes, other than chronic swelling of the ankles, had not been noted by the patient.

As a child he had often been sent home from school because of aching joints, fever and a feeling of numbness in the hands. In his early teens the numbness and tingling had subsided with no recurrence.

The patient had been separated from the Armed Service in 1945 because of rheumatic fever. A review of records revealed that similar but more severe joint pains and a systolic murmur were present at that time. He performed light manual labor immediately after discharge and noted easy fatigability. Recurrence of fever and joint pains prompted hospitalizations in 1949, 1950 and 1954, at which times the diagnosis of recurrent rheumatic fever was entertained. On one of these occasions, 1950, he was seen by a dermatology consultant and a diagnosis of Angiokeratoma of Mibelli was made.

The same symptom complex prompted hospitalization in 1952. At that time, albumin, casts and red cells were reported in the urine. An electrocardiogram was interpreted as showing left ventricular hypertrophy because of amplitude. Multiple urine cultures were sterile and the maximum concentration recorded on random specimens was 1.025. Phenolsulfonpthalein excretion was 69 per cent in one hour. The patient had a febrile course lasting one week, with no response to aspirin, and a diagnosis of acute and chronic glomerulonephritis was made. Since that hospitalization the patient has been followed up in a Veterans Administration clinic where the urine has consistently shown albumin.

The mother and father, two sisters and six brothers are living and well. A maternal grandmother had diabetes mellitus. The father and one brother, age twenty-three years, have similar skin lesions, first noted in the brother at thirteen years of age. Neither the brother nor the father have any apparent systemic manifestations nor have they required the services of a physician, according to the patient. All attempts to contact and observe the father and brother were unsuccessful. The patient did not resemble other members of the family in his physical appearance.

The patient is married and has two normal children. He is presently employed as a work supervisor, a position which permits avoidance of manual labor and excessive heat. He estimates his fluid intake at 1 to 2 quarts of water daily.

He has worn glasses for reading for the past few years but denied gross visual defects. Occasional bifrontal headaches and slight swelling about the eyes have been noted since age fourteen. Respiratory symptoms have been confined to dyspnea necessitating a slow gait and frequent rests on climbing stairs. In 1953 an increase in edema of the ankles, which had been present since early childhood, had been noted. This

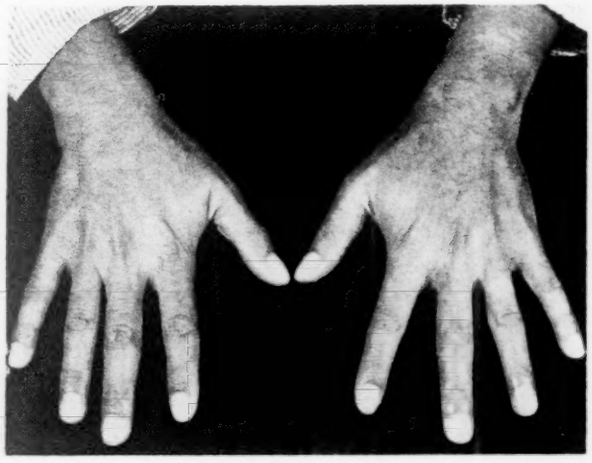


FIG. 3. Pale nails with turtle-back configuration and normal angles at the bases.

was intermittent, being more marked late in the day and aggravated by excessive heat. Fluctuation of weight, seemingly proportional to ankle swelling, was moderate. Frequency of urination and nocturia had been present for fifteen years.

At age seventeen the skin lesions came to notice because of some bleeding. A white area over the lips and a brown mole over the dorsum of the left foot had been observed at an early age. Abnormalities of the nails had been called to his attention in 1952. Scanty sweating had always been noted and in extreme heat only slight axillary, forehead, and forearm perspiration was present.

Physical examination on admission revealed a hypersthenic Latin American man with a simian build and prominent brow. His height was 5 feet 5 inches, weight 146 pounds, blood pressure 130/76 mm. Hg, pulse 100 and regular, respirations 18, and temperature 102.2°F. The head displayed prominence of the supraorbital and malar structures with recession of the frontal bones. Periorbital edema was present. The bulbar and palpebral conjunctivae were peppered with minute red dots lying under slightly thickened, edematous epithelium. These lesions were most pronounced about the puncta of the lacrimal duct. Corkscrew arterioles were seen in the inferior nasal portions of the bulbar conjunctivae. Slit lamp examination of the cornea showed a diffuse haziness in Descemet's membrane. The anterior capsule of the lens was opacified by a white crystalline-like substance, most marked in the inferior nasal quadrants. The discs were normal. The arterioles were slightly narrowed along their entire length and advanced arteriovenous nicking was present, especially at the periphery where corkscrewing of the veins was also noted. Sausage-like dilatations and capillary micro- and macroaneurysms were noted throughout the retina.

The nails of all extremities were turtle-backed, with preservation of the normal angle at the base. The beds were creamy white and the lunula blended indistinctly with the more distal bed. (Fig. 3.)

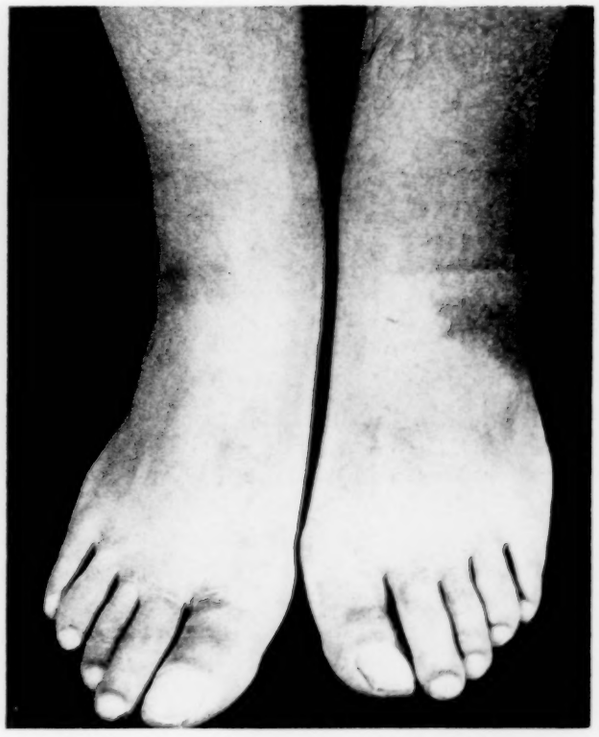


FIG. 4. At this time the patient's ankles were of minimum girth but the fullness is still obvious. A pigmented nevus is seen over the dorsum of the left foot.

The ankles were thickened from the dorsum of the feet to the lower third of the tibiae. The overlying skin was thickened and roughened. The hair over this area was sparse. Pitting could be obtained with moderate pressure. (Fig. 4.)

The skin had a finely marbled ivory, olive brown appearance which escaped detection with artificial light but was quite obvious in natural light. There were many blue to blue-black, flat to slightly raised vascular anomalies measuring 1 to 5 mm. in diameter present over the labial mucosa, extending to the gingival margin, and over the torso, especially the lower half, and the thighs, scrotum and penis. The concentration over the scrotum was marked and verrucous lesions were present. The smaller lesions were flat, the larger ones were slightly raised. None of the lesions bled freely and very few disappeared with pressure. A vitiliginous lesion was noted over the upper and the lower lip on the right. A pigmented nevus was present over the dorsum of the left foot. (Figs. 5 and 6.)

The remainder of the physical examination was within normal limits.

The following laboratory data revealed no abnormalities: Roentgenograms of the chest, long bones, spine, abdomen, kidneys and joints; 24-hour urine determinations of non-protein nitrogen, urea nitro-



FIG. 5. Angiokeratomas over the labial mucosa. These lesions are blue-black and resemble the lesions over the torso.

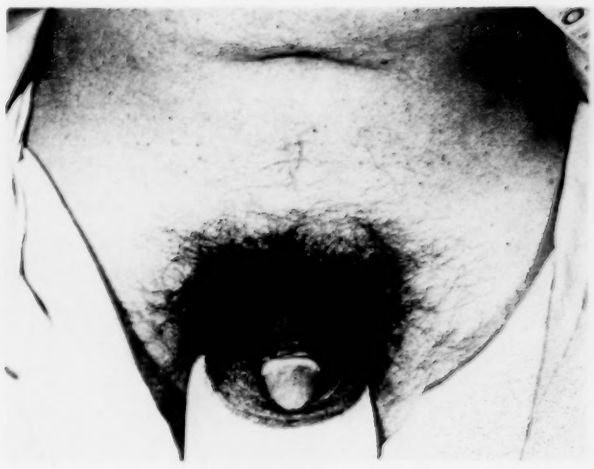


FIG. 6. Angiokeratomas peppered over the torso. Note the tendency to group about the umbilicus. Some verrucous lesions are present on the scrotum and penis.

gen, uric acid, creatinine, creatine, and ammonia; serum Na, Cl, K, CO_2 combining power, Ca, alkaline phosphatase, blood urea nitrogen and creatinine; stools for ova, parasites and occult blood; multiple urine cultures; serum bilirubin, thymol turbidity, cephalin flocculation test, prothrombin time, lipase and amylase; bromsulfalein retention; antistreptolysin titer, serological reactions for syphilis, Rose test, L.E. preparations; and oral and intravenous glucose tolerance tests. The serum total lipids were 550 mg. per cent and 480 mg. per cent; the serum total cholesterol was 155 mg. per cent and 174 mg. per cent. Skin tests with P.P.D., coccidioidin and histoplasmin were negative and febrile agglutinins were less than 1:20.

The serum uric acid was 6.7 mg. per cent on one occasion. The C-reactive protein was 4-plus on admission and within normal limits ten days later. The serum phosphorus was low normal to below normal on three occasions. Serial electrocardiograms were suggestive of left ventricular hypertrophy on the basis of amplitude.

The total white count ranged between 7,000 and 10,000 per cu. mm. with a slight absolute increase in lymphocytes. The average of hemoglobin determinations (by spectrophotometry) was 11.0 gm. per cent and the hematocrit was 38 per cent. The corrected sedimentation rate was slightly increased. The morphology of the red cells appeared normal. The average serum iron was 60 μg. per cent and the average serum iron-binding capacity was 275 μg. per cent. Saline fragility studies showed the control to begin at 0.45 and was complete at 0.36 while the patient began at 0.48 and completed at 0.39. The Coombs' test was negative. Repeated search of the peripheral blood smears failed to reveal abnormal white cells, particular attention being directed to the detection of lipoid-like substance in monocytes.

Multiple urinalyses revealed 2- to 4-plus albumin, with a twenty-four-hour proteinuria ranging from 1.5 to 3.0 gm. Many granular casts, some inclusion casts, rare red and white cells were noted. Of particular interest was the oval-shaped macrophage stuffed with doubly refractile bodies giving the typical Maltese cross appearance by polarized light. These were consistently found in all urine specimens. This cell resembles a mulberry Occasional inclusion casts were seen which contained the same material. (Fig. 2.)

Random specific gravity measurements of the urine ranged from 1.006 to 1.014, and 1.023 was attained with the Fishberg concentration method. Phenolsulfonphthalein excretion studies revealed slight reduction in the excretion in the first specimens, the one-hour excretions being well within normal limits. The twenty-four-hour excretion of amino acids was below normal.

The fractionation of the serum proteins revealed slight elevation of the alpha-1 and alpha-2 globulins and slight reduction of the albumin, beta and gamma globulins.

The course in the hospital was characterized by fever ranging from 100.0 to 100.4°F. in the mornings to 100.6 to 101.4°F. in the evenings for the first nine days. Then the temperature ranged from 97.8 to 99.8°F. for four days followed by temperatures between 98.0 and 98.6°F. for the remainder of hospitalization. Aching of the joints persisted with fever and subsided with return to normal temperature. Aspirin had no effect on the fever or aching. On the third hospital day a definitive diagnosis was made and from that time on no medication was given and the patient ate a regular house diet.

During the afebrile period the patient was placed in a heat cabinet to test the sweating apparatus. After seven minutes he felt very weak and was removed from the cabinet at which time no sweating was noted.

The patient stated that axillary sweating appeared after leaving the room.

At the patient's request biopsy procedures were limited to the initial skin biopsy. He was discharged from the hospital receiving no medications and when seen one month later had had no recurrence of fever, but the girth of the ankles, which had been of minimal size when hospitalized, had increased markedly in diameter. He felt better in general, and attributed this to the installation of air conditioning in his place of work.

It is believed that the abnormalities of the skin, eyes, ankles, electrocardiogram, urine, sweating apparatus and nails, peripheral blood and retinal vessels are all manifestations of the basic disease and constitute a distinct entity. The symptoms of fatigue, dyspnea, fever, aching in the joints, parasthesias of the extremities and heat intolerance are common to the full-blown clinical picture.

SUMMARY

Angiokeratoma corporis diffusum universale, or Fabry's disease, is a systemic disease probably due to a hereditary defect in lipoid metabolism. The syndrome is easily recognized by its typical skin manifestations. To date all cases have occurred in males. Probably fewer than thirty cases have been recorded in the world literature.

The pathological changes are widespread in the media of the blood vessels, the arteries of the kidneys showing the most pronounced changes. Vacuolization of the smooth muscle with replacement by doubly refractile bodies which, when analyzed chemically, resemble sphingomyelin in many respects but differ in solubility, is the basic defect. Similar lesions have been demonstrated in the skin, smooth muscle of the gastrointestinal tract, autonomic ganglia, reticuloendothelial cells and various endothelial cells. A characteristic cell has been found in the bone marrow and the urine.

The syndrome has ophthalmologic, cardiovascular, renal, pulmonary, epidermal and gastrointestinal manifestations. Symptoms of fever, vague aching, sweating abnormalities, parasthesias, swelling of the ankles and eyes, nocturia and frequency, intolerance to heat and cold, and skin lesions may bring the condition to the attention of the physician. The syndrome may be easily recognized by knowledge of the component lesions. There is no treatment at the present time.

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The Demonstration of Intranuclear Inclusion Bodies in Sputum from a Patient with Varicella Pneumonia*

BUERK WILLIAMS, M.D. *and* THOMAS H. CAPERS, M.D.
Dallas, Texas

CHICKENPOX is generally considered to be a common and benign childhood disease. The virus is thought to be widely disseminated throughout the body and in rare instances visceral manifestations have developed in children, occasionally even resulting in death [*1,2*]. Although adults are considered much less susceptible to varicella than children [*3*], complications are much more likely to develop, especially varicella pneumonia. Since Waring et al. reported two cases of adult varicella pneumonia in 1942 [*5*], approximately sixty cases have been introduced into the literature to date [*6*]. Many of these cases have been fatal; the multiple visceral, especially the pulmonary pathological findings have been thoroughly described by various authors [*5,7–10*]. It is evident that varicella pneumonia is a distinct and serious clinical entity, not as uncommon as once thought.

The diagnosis of varicella pneumonia has been made by a combination of clinical signs and symptoms together with the findings on the chest roentgenogram. Some radiologists [*11–14*] claim that the diagnosis can be made from the clinical information and these roentgenographic findings, which are frequently described as a bilateral diffuse mottled miliary infiltration. However, some eighty different disease entities have been reported to be capable of producing this roentgenographic appearance [*15,16*]. There is then a definite need to establish a positive etiologic diagnosis of the type of pneumonia when it develops in association with varicella. An adequate solution to this problem would be a positive pulmonary cytologic diagnosis. A review of the literature failed to reveal any positive cytologic diagnosis of varicella pneumonia except from postmortem pathologic examination. This case is presented because the "Type A intranuclear inclusion bodies" pathognomonic of varicella were successfully recovered and identified from the sputum cells of an adult with varicella pneumonia.

CASE REPORT

A forty-seven year old unemployed white man entered the hospital on March 19, 1958, complaining of extreme shortness of breath of one day's duration. In 1942, following an infection of the upper respiratory tract, a mild episode of shortness of breath and wheezing developed. These asthmatic symptoms continued intermittently, and in 1943 he was discharged from the service. Since that time he has noted slowly progressive dyspnea on exertion and has continued to have intermittent non-seasonal episodes consisting of dyspnea, wheezing and cough. The bouts have slowly increased in frequency and severity and have required hospital admissions on at least five occasions. In 1948 a diagnosis of intrinsic bronchial asthma and emphysema was made. In 1950 denervation of the left pulmonary plexus and decortication of the left upper lobe were performed to relieve symptoms but without benefit. In 1951, 1953 and 1957 acute exacerbations of his symptoms were successfully treated in the hospital with the use of various bronchial dilators, wetting agents and antibiotics. Since October 1957 he had had no major attacks.

One day prior to admission, following an episode of emotional stress, dyspnea, wheezing and a cough developed which was productive of slight amounts of mucopurulent sputum. These symptoms failed to respond to the usual hand nebulizer regimen. The administration of aminophyllin and penicillin by his physician resulted in only transient improvement of his symptoms so on the following day he sought hospital admission. There was no history of fever, chills, hemoptysis or previous infection of the upper respiratory tract prior to this admission. The family history,

* From the Veterans Administration Hospital and The University of Texas Southwestern Medical School, Dallas, Texas.

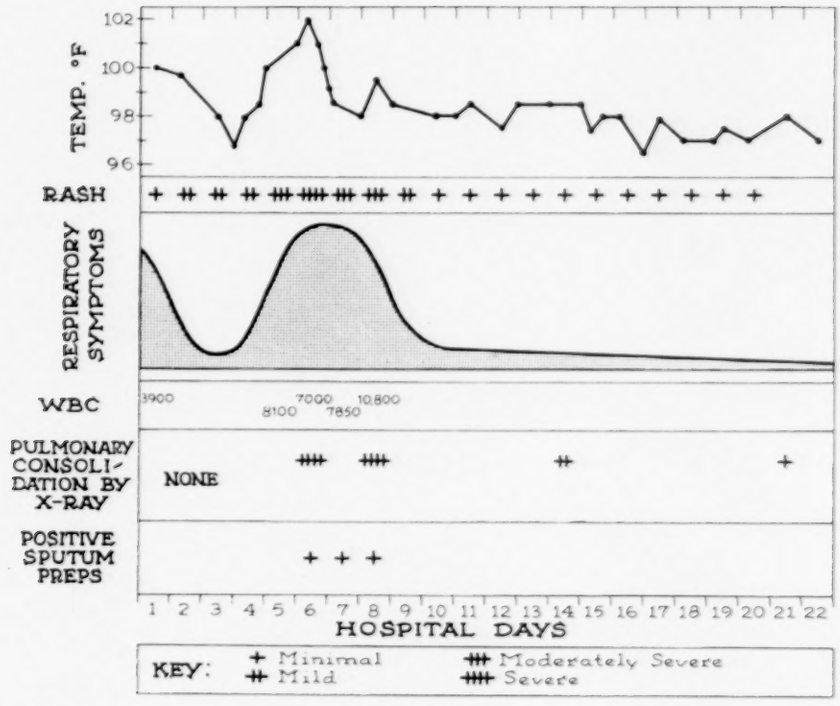


FIG. 1.

past history and review of systems were non-contributory. He believed he had had chickenpox in childhood. He had been treated with penicillin and iodides without reaction in the past.

. On admission, physical examination revealed a well developed, well nourished, cooperative, alert man, in moderately severe respiratory distress. The blood pressure was 120/87 mm. Hg, pulse rate 120 and regular, respirations 26 per minute, temperature 100°F. orally. Examination of the head, neck, eyes, ears and throat was within normal limits. Several teeth were missing; the remainder were in poor repair. Breathing was rapid and labored, with a prolonged expiratory phase and audible wheezes. Except for an old well healed thoracotomy scar along the left fifth rib posteriorly, the thorax was symmetrical. Expansion was fair and bilaterally equal. The lung fields were slightly hyperresonant to percussion bilaterally. The position and excursions of the diaphragms were normal. Breath sounds were slightly diminished in general and diffuse sibilant rales were heard throughout both lung fields. The heart sounds were distant, rapid and regular. There was no cardiomegaly, friction rub or murmur. The peripheral pulses were strong and equal bilaterally. The neck veins were not distended. The abdomen was symmetrical, soft and without scars or tenderness. The liver edge was smooth and non-tender and extended 2 cm. below the right costal margin. No masses or additional organs were palpable. Bowel sounds were active. Examination of the genitalia, rectum, back and extremities revealed no significant abnormalities. Inspection of the skin revealed several erythematous papules approximately 2 mm. in diameter, scattered over the right flank. No additional abnormalities of the skin were noted. There was no remarkable lymphadenopathy. The neurologic examination was within normal limits.

The pertinent laboratory data and course are charted in Figure 1. The chest roentgenogram taken on admission showed pulmonary emphysema and fibrosis with cystic changes in both bases and the residuum of an old left upper lobe thoracotomy but no evidence of active disease was present. The initial asthmatic manifestations improved on symptomatic therapy. The skin rash increased and a rapid increase developed concurrently in the patient's pulmonary symptoms which reached a peak on the sixth day. Varicella pneumonia was diagnosed. (Fig. 2.) He recovered gradually from the pneumonia and a chest roentgenogram five weeks after onset showed complete resolution of the pneumonic infiltrate.

MATERIAL AND METHODS

Sputum samples were collected in 70 per cent alcohol fixative, usually 40 to 50 cc. in volume. The sputum volumes ranged up to 5 cc. and were obtained by deep cough and fixed immediately. These were allowed to fix for at least fifteen minutes and in some cases for twenty-four hours. Smears and cell blocks of the fixed sediment were made. In the case of the skin vesicles, the vesicle fluid was smeared on clean glass

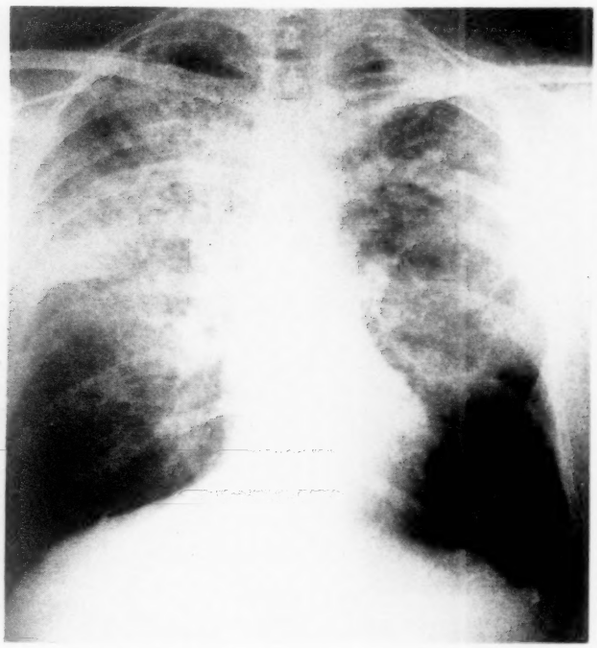


FIG. 2. The chest roentgenogram taken on the sixth hospital day demonstrated diffuse areas of fine nodular infiltrates of variable size throughout both lung fields, with a tendency toward confluency in certain areas, all of which are characteristic of varicella pneumonia.

slides and fixed immediately in half alcohol and half ether. The fixed preparations were stained by the Giemsa method and by the Shorr S-3 technic [*17*], a specific stain for inclusion bodies. Cell blocks were studied after paraffin embedding and staining by both hematoxylin-eosin and Shorr S-3 technics.

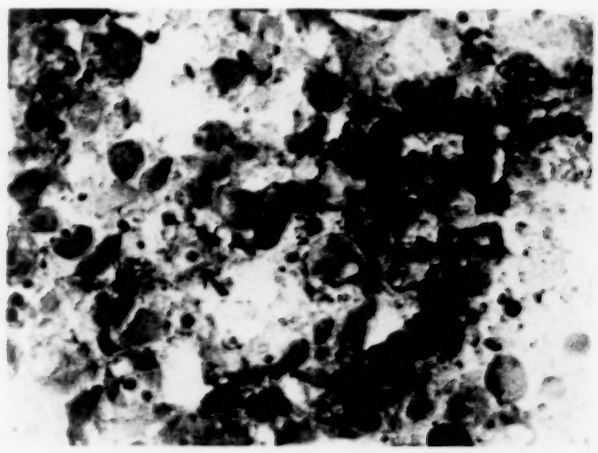


FIG. 3. A photomicrograph of a skin vesicle fluid smear showing several intranuclear inclusion bodies under high magnification. Stained by the Shorr S-3 method.

In the skin vesicle material were found inclusion bodies which were eosinophilic and oval, ranged in size from about 1 to 5 microns in diameter and usually had a homogeneous, refractile appearance. (Fig. 3.) In the Shorr stain of sputum cell blocks and smears, the inclusion bodies were reddish brown or red and were in sharp contrast to normal nuclei which stained bluish to bluish black. Frequently there was a halo about the inclusion body. The same inclusion bodies were seen in intranuclear and intracytoplasmic locations in the basal cells and columnar cells of the sputum sediment. (Fig. 4, left.) They were most easily seen in the sediments in the cell block preparations stained by the Shorr technic.

In one or two cells, apparently non-keratinizing

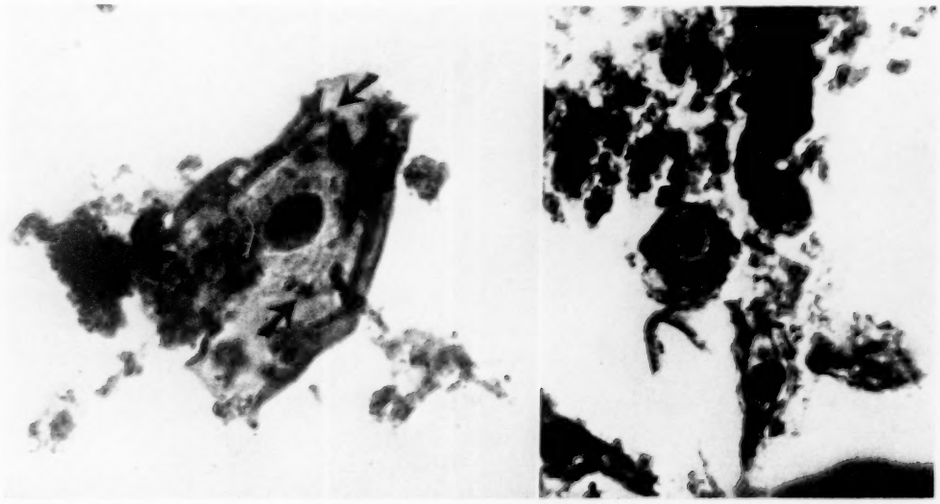


FIG. 4. *Left*, a photomicrograph of a sputum cell block showing a columnar cell with an intranuclear inclusion body and a chromatin border at the nuclear membrane. High power, stained by the Shorr S-3 method. *Right*, a photomicrograph of sputum smear showing a single non-keratinized squamous cell containing cytoplasmic "Guarnieri" type bodies. High power magnification, stained by the Shorr S-3 method.

squamous cells, there were small cytoplasmic inclusions, oval in shape, with a slightly bipolar appearance, eosinophilic in staining quality, situated in the cytoplasm. In one cell the small inclusions, which represented Guarnieri-type bodies, exhibited early invasion of a columnar cell nucleus. (Fig. 4, right.) The giant cells of varicella pneumonia described in autopsy material by Frank [9] and by Lendrum [18] were not seen in our preparations.

COMMENTS

Certain features of this case are worthy of special mention. Based on the patient's statement that he had had varicella during childhood and the early atypical appearance of the skin rash, the initial impression was a penicillin reaction and steroid therapy was therefore started. This therapy undoubtedly contributed to the dissemination of his infection. Fortunately however, an accurate clinical diagnosis was made and steroids were discontinued before a fulminating process developed. Although no detrimental effects resulted from the use of steroid therapy in one recorded adult during a varicella infection [19], there is now ample evidence to the contrary, namely, that, at least in children, steroid therapy superimposed upon a varicella infection enhances the infection and results in an acute and fulminating illness, ending in death [20,21].

The onset of pneumonia in this case was very rapid. The clinical signs and symptoms, laboratory data, roentgenographic findings and overall course during the pneumonia correspond closely to the well documented cases already recorded in the literature [6,19,22]. Secondary bacterial infection was prevented by the administration of the tetracycline which was not believed to have any direct effect on the varicella virus.

We believe that this is the first case on record in which, by the study of sputum smears and sediments, intranuclear and intracytoplasmic inclusion bodies have been demonstrated in living patients with varicella pneumonia. Examination of sputum sediments in patients suspected of having varicella pneumonia offers a simple and valuable procedure in differentiating varicella pneumonia from other pneumonitides.

SUMMARY

A case is presented in which the diagnosis of varicella pneumonia was confirmed by the recovery and identification of Type A intranuclear inclusion bodies from cells in the sputum.

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Jaundice Due to Prochlorperazine (Compazine)*

FRANK A. SOLOMON, JR., M.D. *and* FRANCIS A. CAMPAGNA, M.D.
San Francisco, California

THERE have been many reports of intrahepatic obstructive jaundice following the administration of an apparently heterogeneous group of medications since Hanger and Gutman [*1*] first elaborated its occurrence with arsphenamine in 1940. Some fifteen drugs have been described in which jaundice has occurred as a complication [*2*], but none has evoked the widespread comment that has been given to chlorpromazine (Thorazine®) since its introduction. To this time we have not found any documented reference to jaundice as a complication of prochlorperazine (Compazine®), although a communication from the manufacturers indicates that this drug has been given to "over one million patients" and "while jaundice has been reported in a few instances it has not been possible to definitely attribute this condition to the use of the drug" [*3*]. It is for this reason that the following case is reported.

CASE REPORT

The patient was a housewife of Italian extraction born in California in 1908. Her husband and one child are living, the latter having had asthma since the occurrence of pertussis in childhood. Her mother was well, and the father had died of "rupture of a large blood vessel" at forty-three years of age. Two aunts had had cancer. The patient's previous medical experiences had been confined to a "running ear" at the age of twenty-two and appendectomy at the age of twelve. Her opening statement when she was first seen in May 1956 for nervousness and fatigue was "all my life I have done too much," and "I hate to see my house dirty." After two years of menstrual irregularity she had skipped three periods. The reappearance of vaginal bleeding had prompted consultation. There had been mild flushing and sweating, aching of the legs and puffiness of the ankles at the end of the day. She had used Metamucil® to improve bowel function and had taken gelatin and a vitamin preparation on the advice of a friend.

Her habits were very moderate; she used no tobacco, had two cups of coffee daily and drank a glass of wine with her main meal. Dietary habits included three meals and no essential omission of food.

The patient was 5 feet, 5 inches tall and weighed 125 pounds. The blood pressure was 120/80 mm. Hg. There was a scar on the left membrana tympani. The uterus was retroverted. Physical examination was otherwise not significant. The hemogram, urine and roentgenogram of the chest revealed no abnormalities.

Within a week of administration of a prescription containing 20 mg. of phenobarbital and 0.5 cc. of tincture of belladonna a pruritic, erythematous eruption of the ankles, legs and arms developed. The condition disappeared promptly on substituting 200 mg. of meprobamate. However, this was quickly changed to administration of liquid hydroxyzine (Atarax®) because the patient stated that "pieces seemed to stick in my throat." One month later, in spite of persistent hot flushes, the patient decided she preferred taking no medication. In particular she declined any hormonal support stating she had heard "this will prolong the 'change' and may cause cancer."

One year later on June 20, 1957, she presented herself for examination of a tumor she had found only the day before in the left breast. She weighed 118 pounds. Except for the findings in the breasts the examination was not significantly different. In the left breast, as the patient indicated, there was a hard, movable mass in the upper outer quadrant, 2 by 4 cm. in size, and there were several moderate-sized, axillary nodes. In the right breast in the extreme upper, outer quadrant there was a discrete firm, freely-movable nodule 1 cm. in size; no nodes were palpable in the axilla.

On June 25 a left radical mastectomy was performed. The permanent section revealed adenocarcinoma in the tumor and axillary lymph nodes. The 1 cm. nodule was removed from the right breast; tissue sections showed adenocarcinoma, and on June 28 right radical mastectomy was performed. One liter of blood was administered at the first operation and 500 cc. at the second.

On June 24 and June 25 she received 0.25 gm. of

* From the Department of Medicine, St. Mary's Hospital, San Francisco, California.

TABLE 1

LABORATORY FINDINGS

Data	August					September		October	November
	7	12	13	19	30	9	27	11	6
Urine	15–20 white blood cells	.....	.....	....	...	...	....	.....	....
Red blood cells (cu. mm.)	4,540,000	.....	.....	....	...	...	....	....	....
Hemoglobin (gm. per cent)	13.5	.....	.....	....	...	...	....	....	....
White blood cells (cu. mm.)	6,300	.....	.....	....	...	...	....	....	....
Thymol turbidity (units)	4	.....	.....	....	...	...	....	....	....
Serum albumin (gm. per cent)	4.4	.....	.....	....	...	...	....	....	....
Serum globulin (gm. per cent)	3.2	.....	.....	....	...	...	....	....	....
Prothrombin time	14 sec., control same	.....	.....	....	...	...	....	....	....
Alkaline phosphatase (units)	164 (repeated)	16	Liver biopsy	3.7	...	...	....	....	....
Serum bilirubin, total (mg. per cent)	18	19.2	18	12.2	6.6	3.6	1.4	1.05	0.95
Serum bilirubin, direct (mg. per cent)	.....	10.8	10.6	4.7	4.8	2.9	0.95	0.7	0.3
Serum cholesterol, total (mg. per cent)	.....	243	.....	....	...	...	....	....	....
Cholesterol (per cent esters)	.....	35	.....	....	...	...	....	....	....
Urine urobilinogen (mg./24 hr.)	.....	.....	Negative	22		...	....	....	....

chloral hydrate to induce sleep; nightly between June 26 and July 8 she received 0.100 gm. of pentobarbital sodium (Nembutal®), and between July 9 and 19 0.500 gm. of glutethimide (Doriden®), was given. Preoperative medication on June 25 consisted of meperidine (Demerol®) and scopolamine. Between July 1 and July 3 she received a total of 40 mg. of prochlorperazine (Compazine) given as 5 mg. tablets every four hours as necessary for nausea.

X-ray therapy was begun on July 11 and continued in the outpatient department after hospital discharge on July 19. She received a total of 2,000 r by August 5. On July 31 she was given a prescription for twenty-four tablets of prochlorperazine (Compazine) 5 mg. each to be taken before meals for nausea if necessary. She did not start the prescription until August 1 and had taken twelve tablets when the x-ray therapist noted that the patient was jaundiced at her regular appointment on August 5. The medication was stopped and she was readmitted to the hospital on August 7 intensely jaundiced. The liver was but slightly enlarged, although quite tender. The surgical scars were well healed; there was no clinical sign of local or remote metastases, and roentgenogram of the chest showed no abnormalities. The urine was dark, the stool light.

The patient was treated with a high carbohydrate, high protein, low fat diet with supplemental vitamins and bed rest. Prednisone, 5 mg. four times daily, was added to the therapy on August 14. She was discharged from the hospital August 22 continuing restricted activity, diet and prednisone. The prednisone was gradually reduced and finally discontinued on September 9. By October 11 there was no clinical sign of jaundice and on November 18 bilateral oophorectomy was performed without incident. In May she weighed 127 pounds, felt well, and there was no clinical or roentgenographic evidence of recurrence.

The laboratory studies made during the course of the jaundice are to be found in Table 1. Figure 1 is a photomicrograph of a biopsy specimen of the liver taken with a Vim-Silverman needle on August 13. It shows changes similar to those described in many

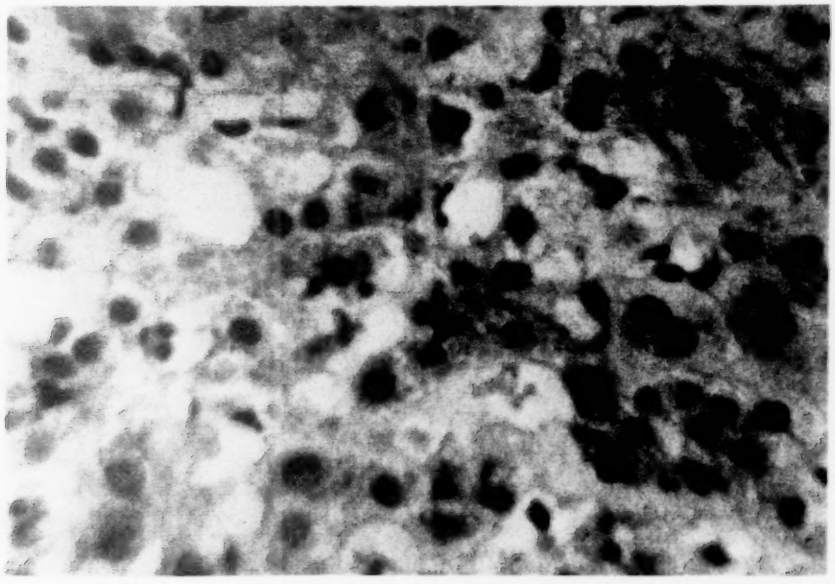


FIG. 1. Photomicrograph of section of liver biopsy showing distention of bile capillaries with inspissated bile and infiltration with lymphocytes and eosinophils.

reports of chlorpromazine jaundice. There is distention of the bile capillaries with areas of bile inspissation and infiltration with lymphocytes and some eosinophils.

COMMENTS

Several facts about this case are interesting. In the first place, it lends some support to the allergic theory of pathogenesis, for the patient's son had asthma, she had previously shown a reaction to medication (probably phenobarbital), and the jaundice appeared promptly with a second course of the prochlorperazine (60 mg.) one month after an initial three-day course totaling 40 mg. Biopsy specimen of the liver showed a picture similar in every way to previously described sections in cases of jaundice involving chlorpromazine [*4*]. In addition, there is to be noted the marked elevation of the serum alkaline phosphatase to which attention has been called in cases of jaundice due to that drug [*5*].

Furthermore, the many possible etiologies for the jaundice in this case only serve to emphasize again the need to include an awareness of the ever widening sphere of liability of drugs in the differential diagnosis. Lastly, as has been pointed out in the comparison of the formulas and reactions of chlorpromazine and promazine, an apparently minor change in the structure (in that instance one Cl ion) may be able to reduce greatly its allergenic attributes. This would appear to be true also of prochlorperazine since there has been no previously reported case of jaundice in spite of what must be by now fairly extensive use.

The mechanism of the production of jaundice in these cases has been well discussed in several excellent articles ([*4–6*], among others) and need not be elaborated further here.

CONCLUSION

A case of jaundice due to prochlorperazine is presented, with pertinent laboratory data including liver biopsy. The jaundice was of the intrahepatic obstructive type resembling in every way that reported in association with the administration of chlorpromazine.

ADDENDUM

Since this report was submitted for publication one other case of jaundice has been reported which is attributed to the administration of prochlorperazine [*1*].

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Hypokalemic Nephropathy in an Adrenalectomized Patient*

JOHN F. WATSON, M.D. *and* FRED H. KATZ, M.D.
Dayton, Ohio *New York, New York*

KUHLMANN et al. reported in 1939 [1] that large amounts of desoxycorticosterone acetate (DOCA®) will produce a syndrome of polyuria, polydipsia, hyposthenuria, diminished responsiveness to Pitressin® and flaccid paralysis associated with hypokalemia in the intact dog. This syndrome was subsequently reproduced in the intact rat [2] and man [3] by either large doses of DOCA or a low potassium diet. In 1941 Liebow et al. [4] observed that in mice a potassium-deficient diet produced characteristic renal lesions which were subsequently duplicated by Durlacher et al. [5] by the administration of DOCA. The mechanism of this syndrome was not understood, however, until the relationships between potassium depletion, the renal lesions and the clinical picture were integrated into one clinical pathological entity by the separate studies of Conn [6], Relman and Schwartz [7], Black and Milne [8] and Oliver et al. [9]. This syndrome is now termed hypokalemic nephropathy. The pathologic condition has not been reported previously in an adrenalectomized animal or man, nor is the mechanism of the polyuria and polydipsia completely understood. It is the purpose of this report to present a case of this syndrome occurring as a complication of replacement therapy following bilateral total adrenalectomy for Cushing's syndrome, and to discuss the possible mechanisms of the pathogenesis of the symptom complex.

CASE REORTT

M. W. (P. H. No. 1318450), a forty-four year old white woman, was essentially well until 1954 when, coincident with a weight gain from 180 to 227 pounds, she became irritable and easily fatigued. There was fullness, flushing and hirsutism of the face, central obesity, wasting of the extremities, and associated weakness of the legs on prolonged standing or walking and difficulty in rising from a sitting position. In January 1955 she had hypertension with systolic pressures over 200 mm. Hg, and diabetes mellitus poorly controlled on diet and 10 to 30 units of protamine zinc insulin per day. Neurological examination in 1955 showed asymmetrical weakness of the leg muscles, greater distally. Vibratory and position sense were absent distally in both lower extremities. The lumbar spine showed generalized osteoporosis on x-ray examination. Later in 1955 she began to have urinary frequency and dribbling, and marked constipation. Re-examination revealed facial telangiectasia and cardiomegaly. The patellar reflexes were diminished and the Achilles reflexes absent, with a negative Babinski sign.

Her neurological symptoms increased, with numbness of the feet and occasional urinary incontinence. By July 1956 she had frequent falls associated with rib fractures, and finally she became unable to walk without support. In August 1956 she was examined at the New England Deaconess Hospital. Neurological examination was as before except for distal leg hypesthesia to all modalities. On lumbar puncture the cerebrospinal fluid was found to contain 1 lymphocyte/cu. mm., protein 92.5 mg. per cent, and chloride 115 mEq./L. Urinary 17-ketosteroids were 19.7 mg./twenty-four hours (normal up to 15 mg.) and urinary corticoids 8.5 mg./twenty-four hours (normal 4 to 7 mg.). The diagnosis of Cushing's syndrome was made and two-stage bilateral total adrenalectomy was performed. The left adrenal weighed 6.7 gm. and the right 8.3 gm. Histopathologic study showed normal adrenal tissue with slight lymphocytic infiltration. She had a benign postoperative course and was discharged with adrenal replacement therapy of 37.5 mg. of cortisone per day, and 10 mg. of DOCA per week administered intramuscularly. Her blood pressure returned to 130–150/70–90 mm. Hg and the neuropathy began to improve.

In October 1956 she was admitted to the Good Samaritan Hospital, Troy, New York, with adrenal insufficiency precipitated by a respiratory infection. Her serum sodium was 116 mEq./L., serum chloride 81.2 mEq./L., and serum potassium 4.02 mEq./L. She responded to intravenous administration of fluids and therapy with hydrocortisone. Following this

* From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital, New York, New York.

TABLE 1

CHRONOLOGICAL SUMMARY OF LABORATORY STUDIES, TREATMENT, INTAKE AND OUTPUT

Date (1957)	Sodium (mEq./L.)	Potassium (mEq./L.)	Chloride (mEq./L.)	CO_2 (mEq./L.)	Blood Urea Nitrogen (mg. %)	Cortisone (mg.)	Hydrocortisone (mg.)	9-α-fluorohydrocortisone (mg.)	Supplementary Potassium (mEq.)	Intake (cc.)	Urinary Output (cc.)
3/25	150	5.5	104.2	....	10	150	...	1/0	...	....	....
						↓		↓			
4/15	143	2.3	....	....	...	50	200	1/0	...	3600	1375
4/16	....	....	92.3	....	...	75	200	1/0	...	3425	2250
4/17	145	2.0	91.4	....	...	50	350	1/0	...	5800	4025
4/18	....	....	....	....	...	none	150	1/0	40	7900	7265
4/19*	140.4	1.9	100.0	29.2	16	150	100	1/0	65	4250	4300
4/20	150	2.07	....	35.5	...	50	....	none	75	2850	3495
4/21	....	....	....	....	...	50	...	none	105	3400	2715
4/22	143.7	3.7	....	36.0	...	30	...	none	75	4050	4405
4/23	143.1	4.5	99.1	33.2	...	30	...	none	...	3225	4107
4/24	139.1	4.7	97.8	31.4	13	30	...	none	...	4940	3555
4/25	133.5	4.7	102.0	29.1	...	30	...	0/1	...	2800	2190
4/26	140.0	4.9	106.0	27.8	...	30	...	0/1	...	4220	2520
4/27	138.8	4.75	....	....	...	30	...	0/1	...	2700	1190
4/28	....	....	....	....	...	30	....	0/1	...	2910	2480
4/29	142.9	4.8	....	....	...	30	....	0/1	...	3340	2080
4/30	138.5	4.8	....	....	...	30	...	0/1	...	2890	2600
5/1	....	....	....	....	...	30	...	none	...	3120	1660
5/2	....	....	....	....	...	30	...	0/1	...	3120	2350
2/5/58	140.2	4.5	114.7	25.2	21†	30	...	0/1 Q2da.	...	....	....

* Transfer to Presbyterian Hospital.

† Within normal limits for autoanalyzer used.

episode almost complete paraplegia developed, with an atonic urinary bladder and fecal incontinence. Because of recurrent episodes of fever, hypotension and diarrhea, she was readmitted to the New England Deaconess Hospital at the end of December 1956. On repeat lumbar puncture the cerebrospinal fluid was found to contain 1 white cell/cu. mm., protein 88 mg. per cent, sugar 72 mg. per cent, and chloride 122 mEq./L. The peripheral neuropathy was diagnosed as Guillain-Barré syndrome.

At that time renal concentration of dye on intravenous pyelography was poor and the blood nonprotein nitrogen ranged between 42 and 29 mg. per cent. Her glycosuria had disappeared. The adrenal insufficiency was considered to be secondary to recurrent retrograde urinary tract infections resulting from urinary retention. Constant indwelling catheter drainage was instituted. The adrenal replacement therapy was increased to 150 mg. of cortisone and 1.0 mg. of 9-alpha-fluorohydrocortisone per day in order to prevent recurrent episodes of hypoadrenalism.

In March 1957 she was admitted to the New York State Rehabilitation Hospital at West Haverstraw, New York, for treatment of the persisting neurological disorder. On April 15, 1957, she suddenly became hypotensive, in association with chills, nausea and increase diarrhea, which were treated with additional intravenous hydrocortisone. Over the following four days there gradually developed striking polyuria and polydipsia (Table 1) and she was transferred to the Presbyterian Hospital on April 19, 1957.

On physical examination the temperature was 99.8°F., pulse 76, respirations 24; blood pressure 200/90 mm. Hg. She had a plethoric facies. The arm and leg muscles were wasted. The heart and lungs were normal. The liver was palpable 2 fingerbreadths below the right costal margin. Neurological examination was essentially as previously described.

The hematocrit was 36 per cent, white blood cells 16,050/cu. mm. with a differential count of 94 per cent neutrophils, 4 per cent lymphocytes and 2 per cent monocytes. The urinalysis showed a specific gravity of 1.010, pH 4.5, no protein, 2-plus reducing substance (dextrose infusion running), no acetone, and occasional white blood cells with epithelial debris. The serum electrolytes were as listed in Table 1. Electrocardiogram was compatible with hypokalemia.

She was considered to have hypokalemic nephropathy. Steroid replacement therapy was reduced and potassium administered in the quantities shown in

Table 1. On April 20 and 21, 1957, she was given a diet containing less than 500 mg. of sodium per day. This resulted in a decrease in urinary volume without change in urinary specific gravity. On April 22 normal sodium intake was resumed and polyuria recurred. By April 23 the urine had become alkaline or neutral and remained so for a week, when it again turned acid. On April 23, 5 units of aqueous Pitressin® administered intramuscularly did not increase the urinary specific gravity above 1.004 or decrease the urinary minute volume. During the first month of hospitalization the urinary specific gravity remained 1.010 or less, even on fluid restriction. Phenolsulfonphthalein excretion was 40 per cent in two hours and the blood urea nitrogen 13 to 20 mg. per cent. The inulin clearance was 33 ml./minute on April 24, and 27 ml./minute five weeks later. The sodium and potassium clearances were: sodium 0.5 ml./minute and potassium 6.0 ml./minute. Arterial oxygen saturation on April 23 and 24 was 86 per cent at a blood pH of 7.41 and 85 per cent at a blood pH of 7.38, respectively. The arterial CO_2 content was 60.5 volumes per cent with a pCO_2 of 49 mm. Hg. When the patient breathed 5 per cent CO_2, the arterial oxygen saturation increased to 94 per cent. Repeated arterial studies on May 10, 1957, when she had recovered from the metabolic alkalosis, revealed an oxygen saturation of 98 per cent with a pCO_2 of 46 mm. Hg.

In May 1957 roentgenograms showed generalized osteoporosis and an old compression fracture of the body of the twelfth thoracic vertebra. The serum calcium was 12.6 mg. per cent, inorganic phosphorus 3.7 mg. per cent, and alkaline phosphatase 9.5 Bodansky units. Bromsulfalein retention was a trace at thirty minutes, and cephalin flocculation and thymol turbidity tests were negative. Hypochromic anemia developed with a hematocrit of 26 per cent and reticulocytes of 2.6 per cent. This was associated with intermittently positive stool guaiac tests. Barium enema was normal. Intravenous pyelography again showed poor concentration of the dye. An intravenous glucose tolerance curve was normal. Lumbar puncture revealed no evidence of subarachnoid block. The total spinal fluid protein was 60 mg. per cent and there were 2 white cells/cu. mm. Electromyography showed features of both a diffuse intrinsic muscular disorder and a neuropathy. There was evidence of active denervation in the paralyzed leg muscles on chronaxie studies, and some muscle groups did not respond at all to direct stimulation. The urinary creatine excretion was 206 mg./twenty-four hours while the patient was eating a creatine-free diet. Left sural nerve biopsy showed marked loss of myelin sheaths and axones. Biopsy of the left gastrocnemius muscle revealed muscle atrophy.

Maintenance adrenal replacement was established at 30 mg. of cortisone per day, 0.1 mg. of 9-alpha-fluorohydrocortisone every other day, and 3 gm. of sodium chloride per day. During May 1957 her course was complicated by mild adrenal crises precipitated by recurrent urinary tract infections with gram-negative bacteria. These episodes were associated with fever, proteinuria, pyuria and, once, elevated blood urea nitrogen. These signs and symptoms responded to intravenous fluids, added cortisone or hydrocortisone and appropriate antibiotics. Her neuromyopathy gradually improved so that she was able to void without an indwelling catheter.

On June 7, 1957, she was returned to the New York State Rehabilitation Hospital. The neurological picture has continued to improve. When last examined in February 1958 she was asymptomatic and had complete bowel and urinary control. Partial strength had returned to the legs, enabling her to begin walking with the aid of hip braces. The right anterior tibial group was the only muscle group still completely paralyzed, and the Achilles reflexes had returned. Hypesthesia to all modalities persisted in both lower legs, but has continued to improve. The blood pressure was 150/90 mm. Hg. Pigmentation of the skin had increased. The serum calcium, inorganic phosphorus, alkaline phosphatase and blood urea nitrogen were now all within normal limits. (For other serum electrolytes see Table 1.) A casual urine specimen revealed a specific gravity of 1.014 with no protein and only an occasional leukocyte. Her hematocrit had risen to 36 per cent.

COMMENTS

It seems clear that the patient had a spontaneously developing Cushing's syndrome associated with a Guillain-Barré type of severe peripheral neuropathy. This association has been reported several times recently [*10–12*].

After three and a half months of large doses of adrenal steroids, following adrenalectomy, the patient became potassium-deficient. This was presumably the result of kaliuresis caused by the mineralocorticoid, although excessive potassium loss from intermittent diarrhea may have contributed. As the patient became potassium-deficient there developed polyuria, polydipsia and hyposthenuria unresponsive to Pitressin, that is, the syndrome of hypokalemic nephropathy.

Since the first observation of this syndrome by Kuhlmann et al. in 1939 [*1*] it has been reproduced experimentally [*2,3*] and found clinically in association with various states of chronic potassium deficiency: namely, low potassium diets [*8*], primary aldosteronism [*6*] and chronic diarrhea [*13*]. Because a reproducible renal lesion has been found in association with chronic states of potassium deficiency [*7*], the symptom complex in recent years has been attributed

to the hypokalemic nephropathy alone. However, in those states which are secondary to excessive mineralocorticoid (DOCA) or aldosterone), there appear to be other important factors which contribute to the syndrome and are illustrated in the case presented.

Several mechanisms for the polyuria induced by mineralocorticoid have been suggested. These include (1) hypernatremia, (2) the hypokalemic nephropathy itself and (3) antagonism to antidiuretic hormone (ADH).

Ragan et al. [*23*] believed the polydipsia to be primary, resulting from hypernatremia. Polydipsia then resulted in polyuria. It is true that in their experiments, and in all subsequent experimental and clinical descriptions, including the present case, the polyuria and polydipsia correlate well with the sodium intake and the serum sodium level. However, polyuria definitely preceded polydipsia in the experiment of Zierler and Lilienthal [*3*]. These workers produced polyuria in a man with myotonic dystrophy by the administration of DOCA. In their balance studies, after an initial period of sodium and chloride retention with weight gain and edema formation, there was a sudden natriuresis, associated with polyuria, followed by polydipsia. Renal function showed no change in filtration rate but there was widespread inhibition of tubular reabsorptive functions.

The tubular lesion of hypokalemia is not alone responsible for the polyuria because, as Ferrebee et al. [*14*] showed, administration of potassium chloride along with the DOCA increased the urinary specific gravity and prevented hypokalemia without abolishing the polyuria. Also in Zierler and Lilienthal's experiment [*3*], as already mentioned, polyuria occurred before hypokalemia developed.

Posterior pituitary extract does not significantly diminish the polyuria. Therefore it has been postulated [*15*] that a direct antagonism exists between DOCA and ADH. However, Stahl et al. have recently shown [*16*] that ADH does function in the presence of excessive DOCA. Their experiments, however, did not exclude some posterior pituitary effect in the production of the polyuria.

It is therefore evident that the mechanisms discussed are inadequate to explain the polyuria.

Since excessive mineralocorticoid administration is not followed by polyuria in the adrenalectomized subject, but results in edema formation instead, an alternate mechanism for the polyuria is suggested. In the intact subject the initial increase in extracellular fluid volume and serum sodium, caused by mineralocorticoid, is followed by a natriuresis and polyuria providing that endogenous glucocorticoid is present. This is supported by the studies of Talbott et al. [*18*] and Garrod et al. [*19,20*] showing that the adrenalectomized or Addisonian subject has a diminished glomerular filtration rate and inability to excrete a water load in the absence of glucocorticoid. The patient reported was receiving glucocorticoid.

In addition to the adequate filtered load, there must be, as Stanbury et al. believe [*21*], an associated inhibition of renal tubular sodium reabsorption at a point proximal to the site of cation exchange. This allows an increased delivery of sodium and water to the distal tubule, permitting continued tubular secretion of potassium while restoring normal sodium balance, thus resulting in polyuria without edema. This inhibition of tubular function is supported by the studies of Zierler and Lilienthal [*3*].

The inability to concentrate the urine in the presence of potassium depletion is the only part of the syndrome directly attributable to the renal tubular lesion produced by hypokalemia. This lesion has been well documented to be reversible with potassium repletion in man by Relman and Schwartz [*7*], who performed serial renal biopsies and function tests. A precise correlation between the location of the renal tubular lesion caused by hypokalemia in rats, and the presently assumed site of "free water" reabsorption and urinary concentration, has recently been observed by Oliver et al. [*9*] in the collecting tubules dissected from such animals, where hydropic changes occurred.

It is of interest that, following recovery from metabolic alkalosis, the arterial saturation and the pCO_2 in the patient reported on had also returned to normal. Arterial unsaturation and CO_2 retention have previously been noted in patients with metabolic alkalosis at this clinic by Drs. Fishman and Goldring [*22*]. It is attributed to alveolar hypoventilation. From a teleologic point of view, this represents a mechanism by which arterial pH is maintained at normal levels. Although complete ventilatory studies could not be carried out on the patient, there was no clinical evidence of pulmonary disease.

It is unlikely that the patient's neuromuscular

disorder had any relationship to her hypokalemia, because the neuropathy definitely preceded the hypokalemia.

SUMMARY

A case of hypokalemic nephropathy apparently induced by the excessive administration of 9-alpha-fluorohydrocortisone to an adrenalectomized subject is described. The well known syndrome of hypokalemia, polyuria, polydipsia and hyposthenuria was seen in this patient.

The mechanisms responsible are discussed. It is suggested that the hyposthenuria is the only defect directly related to the nephropathy; the presence of gluco-corticoids and an inhibition of proximal tubular reabsorption of sodium is necessary for the production of the polyuria.

This syndrome has not been previously reported in an adrenalectomized subject.

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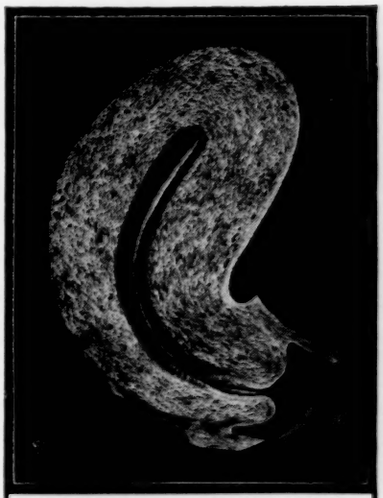
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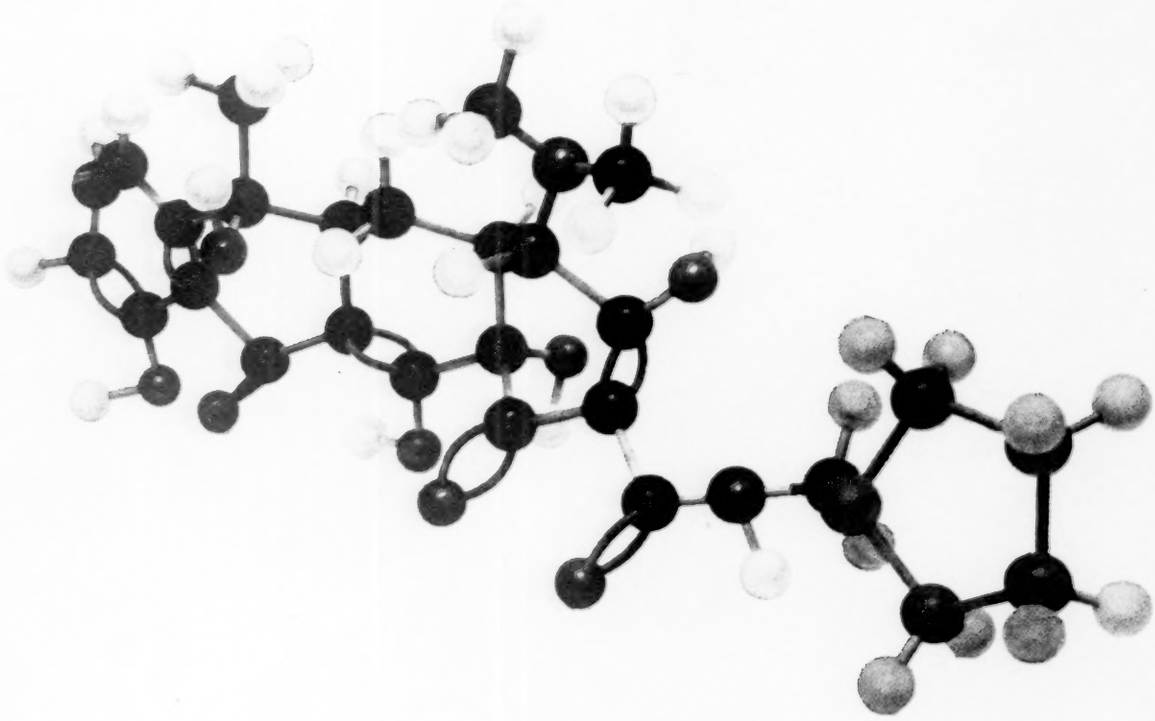


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An important advantage of SYNTETRIN is that the *lowest* blood levels reached before ensuing daily injections are either maintained or increased. This means that antibiotic levels will not drop below those required to inhibit certain pathogens during the course of therapy. Successive blood level peaks generally rise after repeated injections.

Parenteral **SYNTETRIN** is recommended for initial therapy in infections caused by tetracycline-sensitive organisms in:

1. Patients who require frequent force-feeding or special diets based on milk, which interfere with antibiotic absorption.
2. Patients with diseases causing absorption difficulties.
3. Patients unable to take anything by mouth.

1. Gottstein, W. J.; Minor, W. F., and Cheney, L. C.: J. Am. Chem. Soc. **81**:1198, 1959.

for intramuscular injection

SYNTETRIN I.M.

N–(PYRROLIDINOMETHYL) TETRACYCLINE WITH XYLOCAINE®* FOR INTRAMUSCULAR USE

Supplied in dry-fill single dose vials:

SYNTETRIN I.M. '350' contains:		SYNTETRIN I.M. '150' contains:	
SYNTETRIN	350 mg.	SYNTETRIN	150 mg.
Lidocaine	40 mg.	Lidocaine	40 mg.
Ascorbic Acid	300 mg.	Ascorbic Acid	300 mg.

*Xylocaine is the registered trademark of Astra Pharmaceutical Products, Inc. for lidocaine.

for intravenous infusion

SYNTETRIN I.V.

N–(PYRROLIDINOMETHYL) TETRACYCLINE FOR INTRAVENOUS INFUSION

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Detailed information on indications, dosage and precautions is contained in package insert; or, write to Medical Director, Bristol Laboratories Inc., New York, New York.

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BUTAZOLIDIN tablets or the Alka capsules are **equally effective but individually adaptable in a wide range of arthritic disorders.**

Recent clinical reports continue to justify the selection of Butazolidin for rapid relief of pain, increased mobility, and early resolution of inflammation.

Gouty Arthritis: "...95 per cent of patients experienced a satisfactory response..."[1]

Rheumatoid Arthritis: In "A total of 215 cases... over half, 50.7 per cent showed at least major improvement, with 21.8 per cent showing minor improvement...."[2] **Osteoarthritis:** 301 cases showed "...a total of 44.5 per cent with complete remission or major improvement. Of the remainder, 28.2 per cent showed minor improvement...."[2] **Spondylitis:** All patients "...experienced initial major improvement that was maintained throughout the period of medication."[3] **Painful Shoulder Syndrome:** Response of 70 patients with various forms showed "...8.6 per cent complete remissions, 47.1 per cent major improvement, 20.0 per cent minor improvement...."[2]

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Availability BUTAZOLIDIN® (phenylbutazone GEIGY): Red coated tablets of 100 mg. BUTAZOLIDIN® Alka: Capsules containing BUTAZOLIDIN® (phenylbutazone GEIGY), 100 mg.; dried aluminum hydroxide gel, 100 mg.; magnesium trisilicate 150 mg.; homatropine methylbromide, 1.25 mg.

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SPONTIN®

(Ristocetin, Abbott)

A STATISTICAL REVIEW* OF THREE HUNDRED THIRTY-THREE CASES

**Records of Medical Department, Abbott Laboratories, North Chicago, Illinois*

SPONTIN (Ristocetin, Abbott) is a new antibiotic discovered and developed at Abbott Laboratories. Its two components, and B, have been isola line state from the ferr of a new species of *Nocardia lurida*. Bot are active against gra teria and mycobacter mycete was isolated f ple collected from th Gods, Colorado Sp No other culture wh same antibiotic has

The chemical cha ristocetins are not c though they are kn teric substances con phenolic groups a ristocetin A and ris molecules with m the vicinity of 4000 have good stability pH range of bloo SPONTIN is a ly tion, derived fr material, represe ristocetins A an

Antimicrobial tion against gra ganisms, SPON effective than able antibiotics

Against pne cocci (except s cocci) the anti tericidal at th concentration hibits the gro also kills the

This obser for the majo lococci. Ho staphylococ have been t centration s minimum i produce a this reaso SPONTIN i for the treatment of and enterococcal infections.

Cultures of staphylococcus aureus, which are resistant to other antibiotics have been shown to be sensitive to SPONTIN. There has been no case reported in which a staphylococcal or enterococcal strain has exhibited a

SPONTIN

pH range of blood and tissue

SPONTIN is a lyophilized preparation, derived from pure crystalline material, representing a mixture of ristocetins A and B.

Antimicrobial Properties. In its action against gram-positive coccal or- SPONTIN is notably more tly avail-

d strepto- of entero- riably bac- osage. The which in- organisms

holds true s of staphy- e strains of ococci which quired a con- gher than the ncentration to effect. It is for her dosage of recommended staphylococcal tions.

coccus aureus, o other antibi- to be sensitive as been no case taphylococcal or has exhibited a SPONTIN.

that the antibi- NTIN is enhanced gamma globulin. supported by the *vivo* activity of imes greater than from the *in vitro*

estigators* have re- ical response follow- ration of SPONTIN udies have shown a vity on the part of ganism. Satisfactory e may be expected ism requires up to 25 ONTIN for inhibition ollowing table shows nsitivities of different he major pathogenic groups.

Summary and Conclusions

Major use has been treating staphylococcic infections. Of the total 333 cases, approximately one-third was treated for pneumonia; of these over 80% were either cured or improved. About 70% of these pneumonias were caused by staphylococci.

The next largest group included 46 patients with subacute bacterial endocarditis. About 50% of these infections were identified as staphylococcic and a further 15% as enterococcic. Other infections included 38 cases of septicemia, 32 abscesses and 24 patients with osteomyelitis.

The administration of SPONTIN brought about a cure in 60% of all the cases reviewed and improvement in a further 17%.

Side-effects were seldom troublesome when a daily dose of 2 Gm. was not exceeded. The incidence rose as the dosage was increased. The most disturbing side-effect after administration of SPONTIN has been neutropenia. However, in all instances this has responded to either discontinuance of medication or reduction in dose.

109146

New Enzyme-controlled antifungal therapy to meet the growing challenge of Monilial Vaginitis

IN PREGNANCY / IN DIABETES / AFTER ANTIBIOTIC THERAPY–Today, monilial vaginitis is estimated to be a problem in at least 33 per cent of pregnant women and about 10 per cent of nonpregnant females[1]—a rapidly increasing incidence attributed partly to the widespread use of antibiotics.

"Vanay" Vaginal Cream broadens the scope of specific therapy: (1) "Vanay" insures a continuous therapeutic fungistatic effect without danger of local reaction; (2) in addition, "Vanay" restores and maintains a physiologic pH and normal vaginal flora—reducing risk of reinfection.

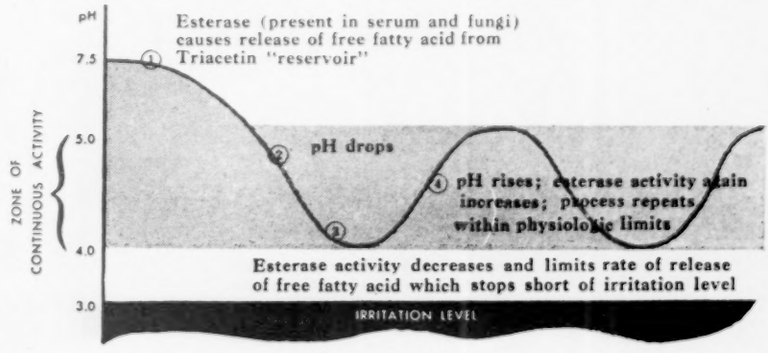
Effective response: Treatment was notably effective in moniliasis, as confirmed by symptomatic relief and post-treatment smears, Assali reports.[2] Marked clinical improvement was also noted in 154 of 206 patients, and in some cases symptoms subsided within a week of therapy.[3]

Other advantages: No monilial resistance demonstrated[4] / prolonged duration of activity[4] / nonsensitizing / nonirritating / nonstaining / odorless.

"VANAY" Vaginal Cream

BRAND OF TRIACETIN IN NONLIQUEFYING BASE

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Indications: specific in monilial vaginitis...adjunctive in trichomoniasis . . . also valuable in nonspecific vaginitis where an acid pH must be restored and maintained.

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Supplied: No. 204-250 mg. Glyceryl triacetate per gram in a nonliquefying base. Combination package: 1½ oz. tube with 15 disposable applicators.

References: 1. Idson, B.: Drug & Cosmetic Industry *84*:30 (Jan.) 1959. 2. Assali, N. S.: Personal communication. 3. Combined results of 18 clinical investigators, Medical Records, Ayerst Laboratories. 4. Kubista, R. A., and Derse, P. H.: Antibiotics & Chemotherapy, to be published. 5. Knight, S. G.: J. Invest. Dermat. *28*:363 (May) 1957. 6. Knight, S. G.: Antibiotics & Chemotherapy 7:172 (Apr.) 1957.

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Niacinamide	100 mg.
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Pyridoxine HCl (B_6)	2 mg.
Vitamin B_{12}	4 mcgm.
Folic Acid	1.5 mg.
Calcium Pantothenate	20 mg.
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Average dose 1-2 capsules daily.

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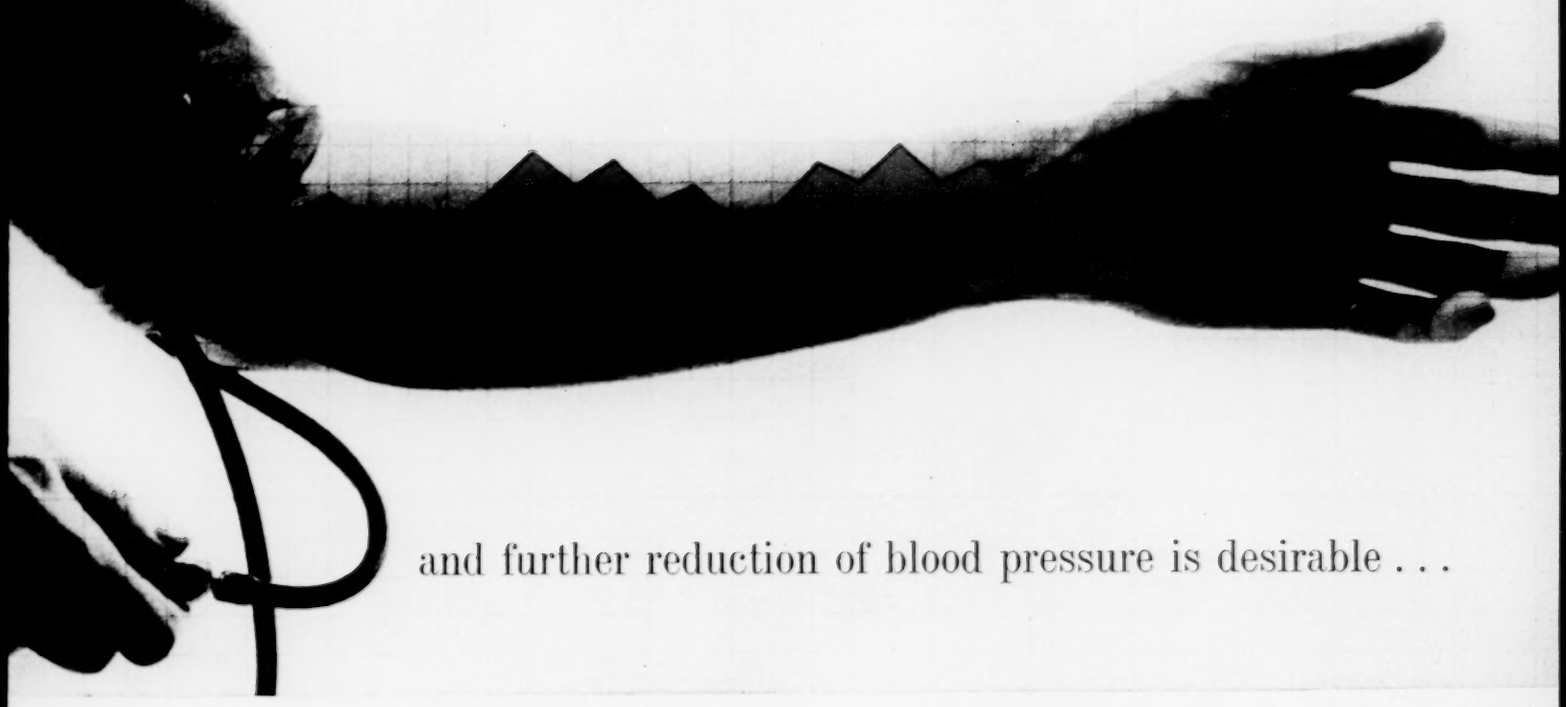
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1. Spies, T. D.: J. A. M. A. 167:675 (June 7) 1958.

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A.M.A. Council on Drugs, New and Nonofficial Drugs: Philadelphia, J. B. Lippincott Co., 1958, p. 285

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pretreatment with 'Diuril', or 'Diuril' and rauwolfia, enhances therapy with 'Inversine'

"Pretreatment with chlorothiazide ['DIURIL'] and rauwolfia reduces the dosage requirement, augments blood pressure response, and moderates certain of the side effects of ganglion blocking agents. Although such basal therapy is advantageous, unnecessary delay must be avoided in establishing ganglion blockade in severe or malignant hypertension."

Beem, J. R., and Moyer, J. H.: Geriatrics 13:378, June 1958

dosage recommendations for new patients

1. *Initiate therapy with 'DIURIL'*
'DIURIL' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day, depending on severity of the hypertension.

2. *Add other agents*
Other drugs (rauwolfia, 'INVERSINE', hydralazine, etc.) are added as necessary and their dosage adjusted according to patient response.

'INVERSINE' is given in the same manner whether used with other drugs or alone. Recommended initial dosage is 2.5 mg. twice a day, preferably after meals. May be increased by 2.5 mg. at intervals of no less than two days until desired response is obtained. In severe or urgent cases, the increments may have to be larger or more frequent, with the largest dose given preferably at noon or in the evening. 'INVERSINE' is extremely potent and should always be titrated according to the patient's orthostatic blood pressure response.

3. *Adjust dosage of all medication*
The patient must be observed frequently and careful adjustment of all agents should be made to determine optimal maintenance dosage.

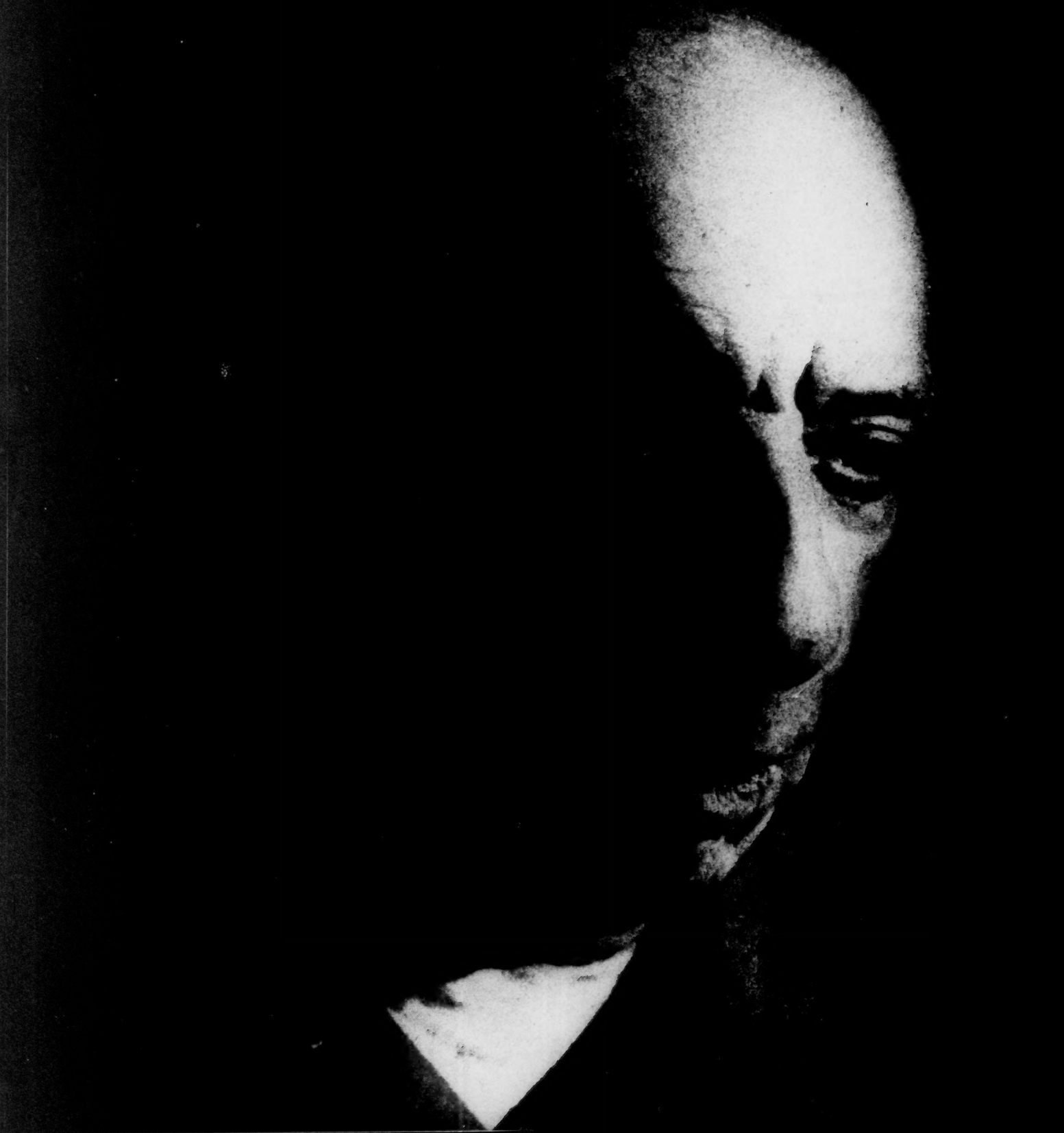
Precautions: Side effects of 'INVERSINE' are essentially the same as those encountered with other ganglionic blocking agents. At the first sign of constipation, vigorous treatment must be initiated immediately since paralytic ileus may result if constipation is unchecked. Patients should be informed how to cope with postural hypotension should this occur. 'INVERSINE' is contraindicated in coronary insufficiency, organic pyloric stenosis and recent myocardial infarction. Additional information on 'INVERSINE' and 'DIURIL' is available on request.

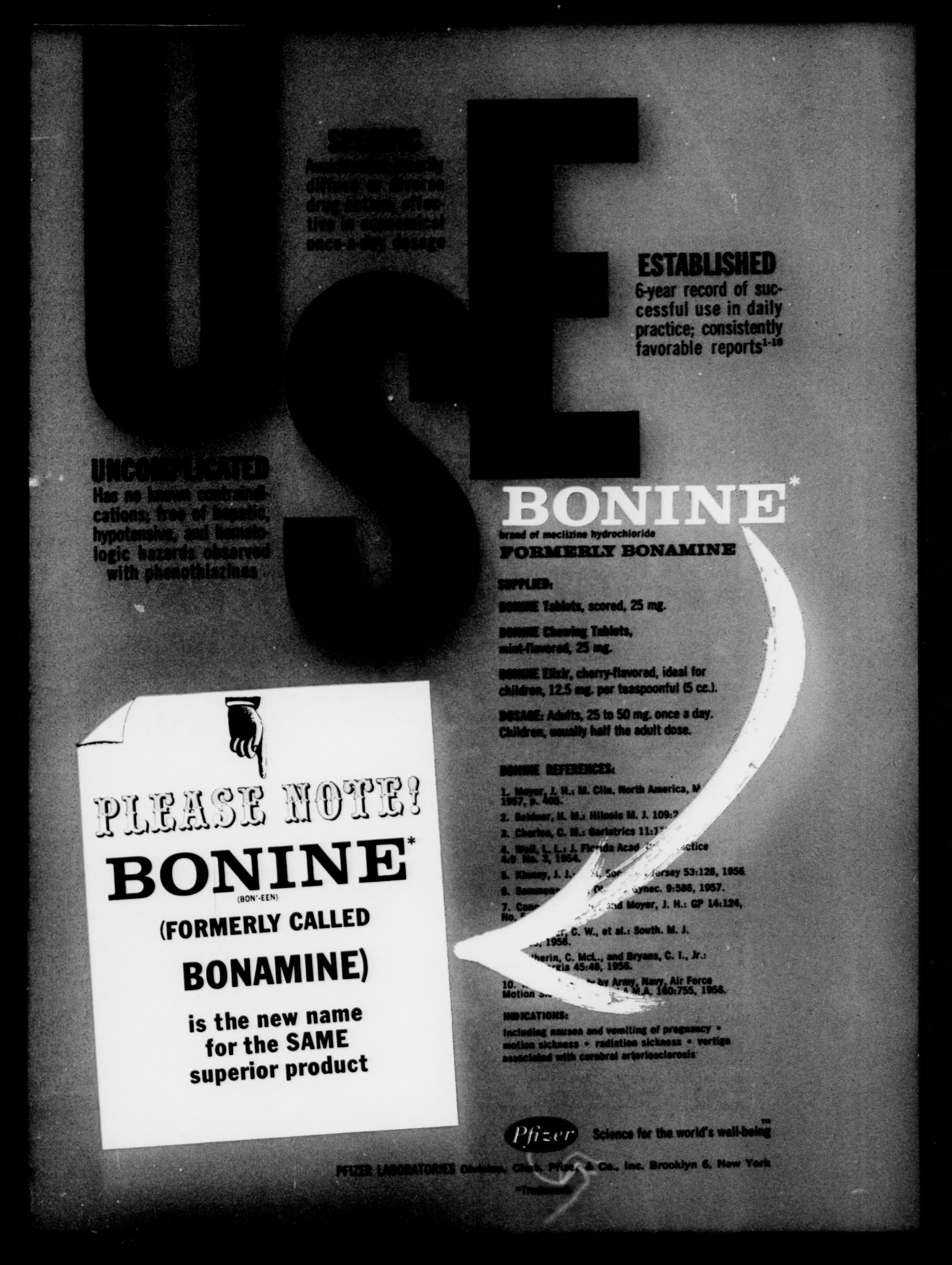
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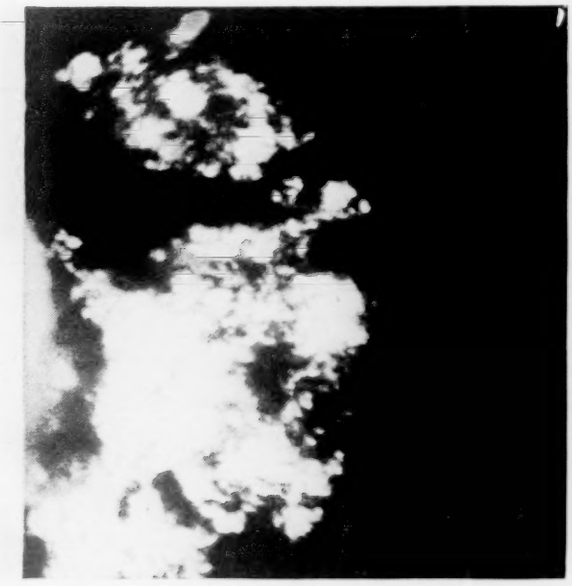
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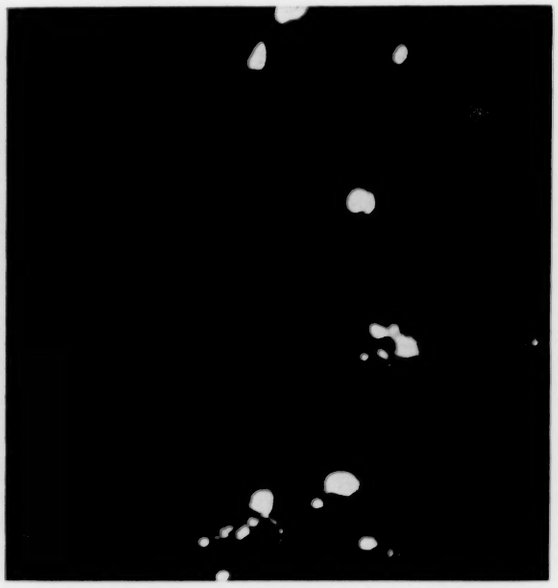
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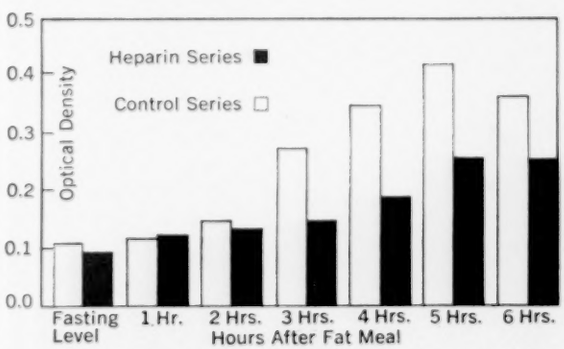
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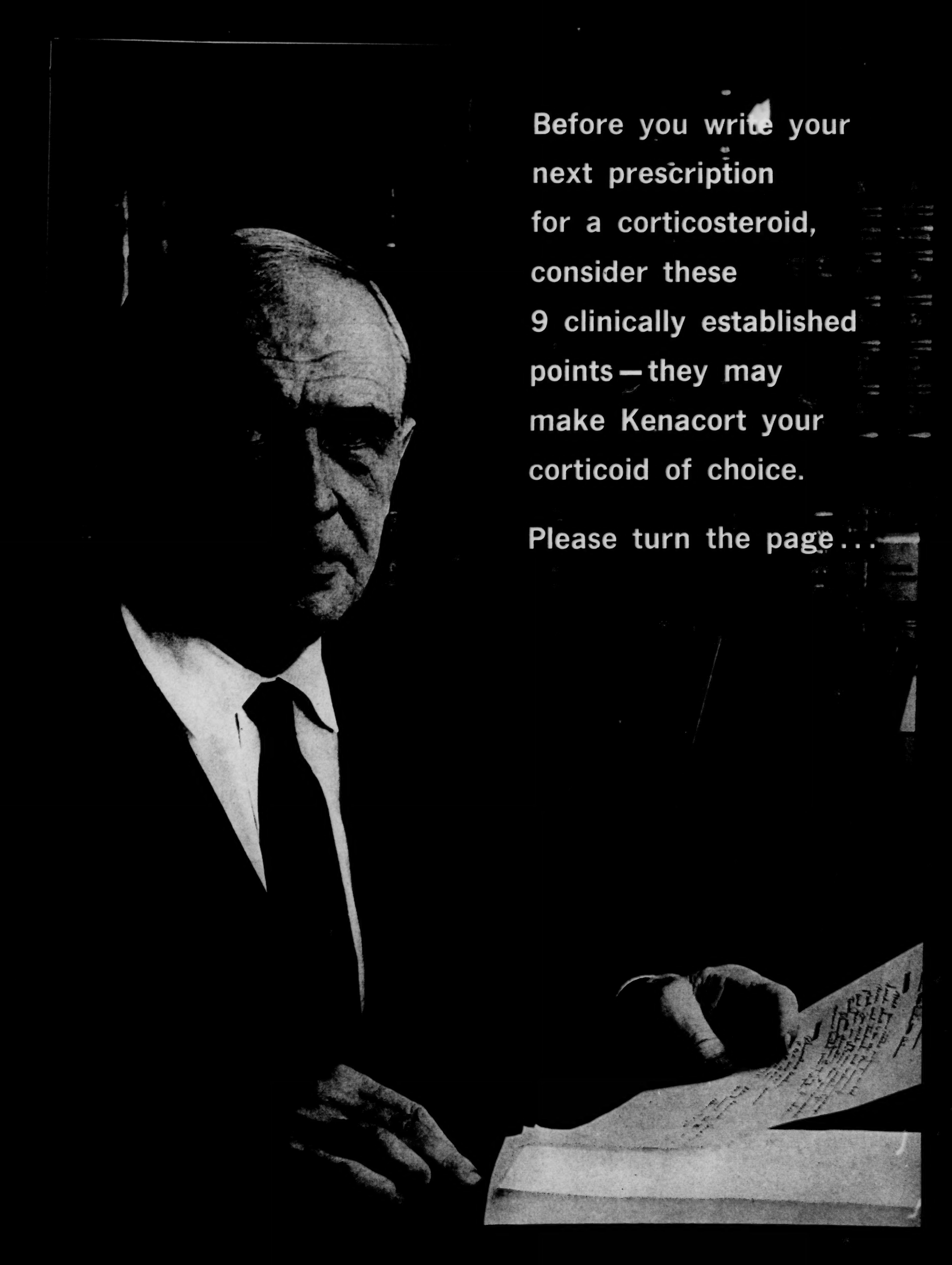
2. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959.



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Allison, J. R., Sr., and Allison, J. R., Jr.:
Monographs on Therapy 3:99 (Oct.) 1958.

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Feinberg, S. M.; Feinberg, A. R., and Fisherman, E. W.:
J. A. M. A. 167:58 (May 3) 1958.

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J. A. M. A. 167:973 (June 21) 1958.

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Council on Drugs:
J. A. M. A. 169:257 (Jan. 17) 1959.

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Bongiovanni, A. M.; Mellman, W. J., and Eberlein, W. R.:
J. Pediat. 53:3 (July) 1958.

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Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.:
J. A. M. A. 167:959 (June 21) 1958.
Bernsten, C. A., Jr., and others:
New York Rheumatism Association, Annual Meeting, New York, April 9, 1959.

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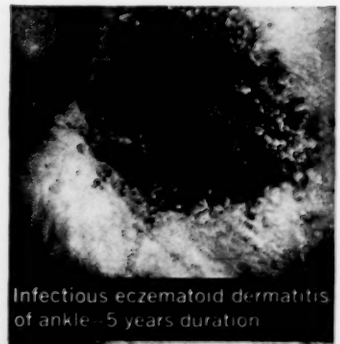


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References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H., Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R.F., and Hallett, J.J.: Monographs on Therapy, 3:153 (Nov.) 1958. • 6. Smith J.G., Jr.; Zawisza, R.J., and Blank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957.

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1. Bellet, S.; Finkelstein, D., and Gilmore H.: A.M.A. Archives Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.
3. Finkelstein, D.: Penn. Med. J. 61:1216, 1958.

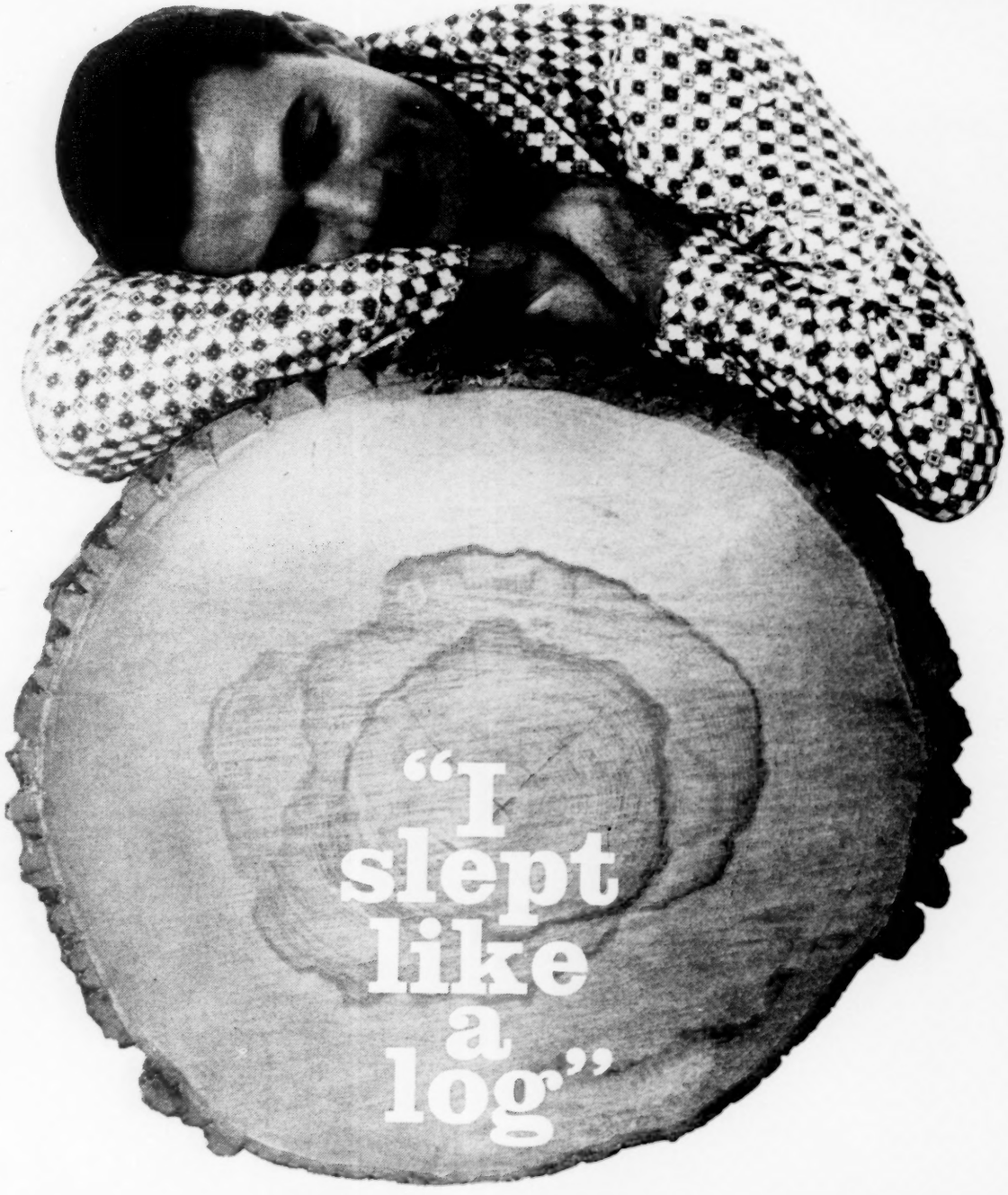
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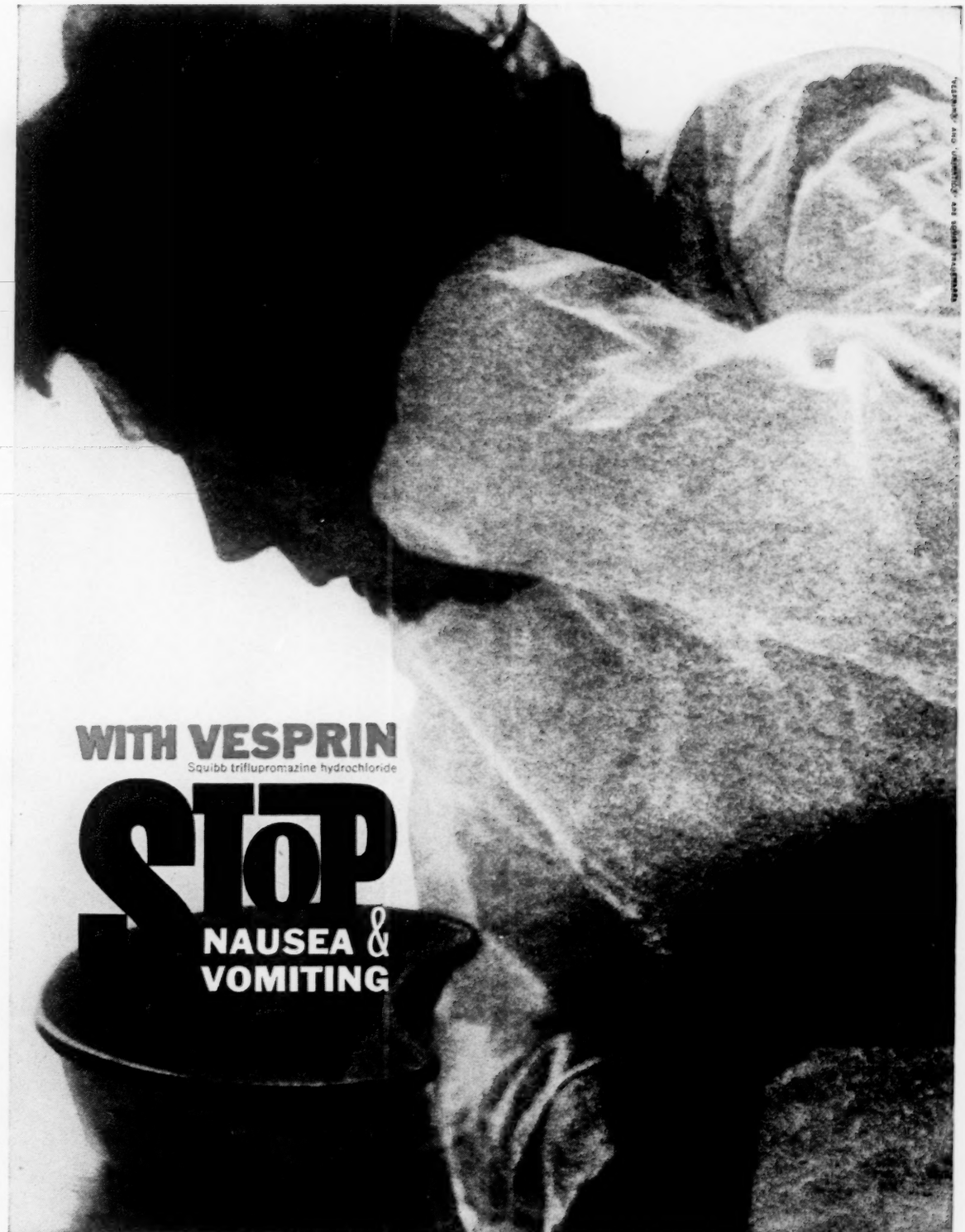
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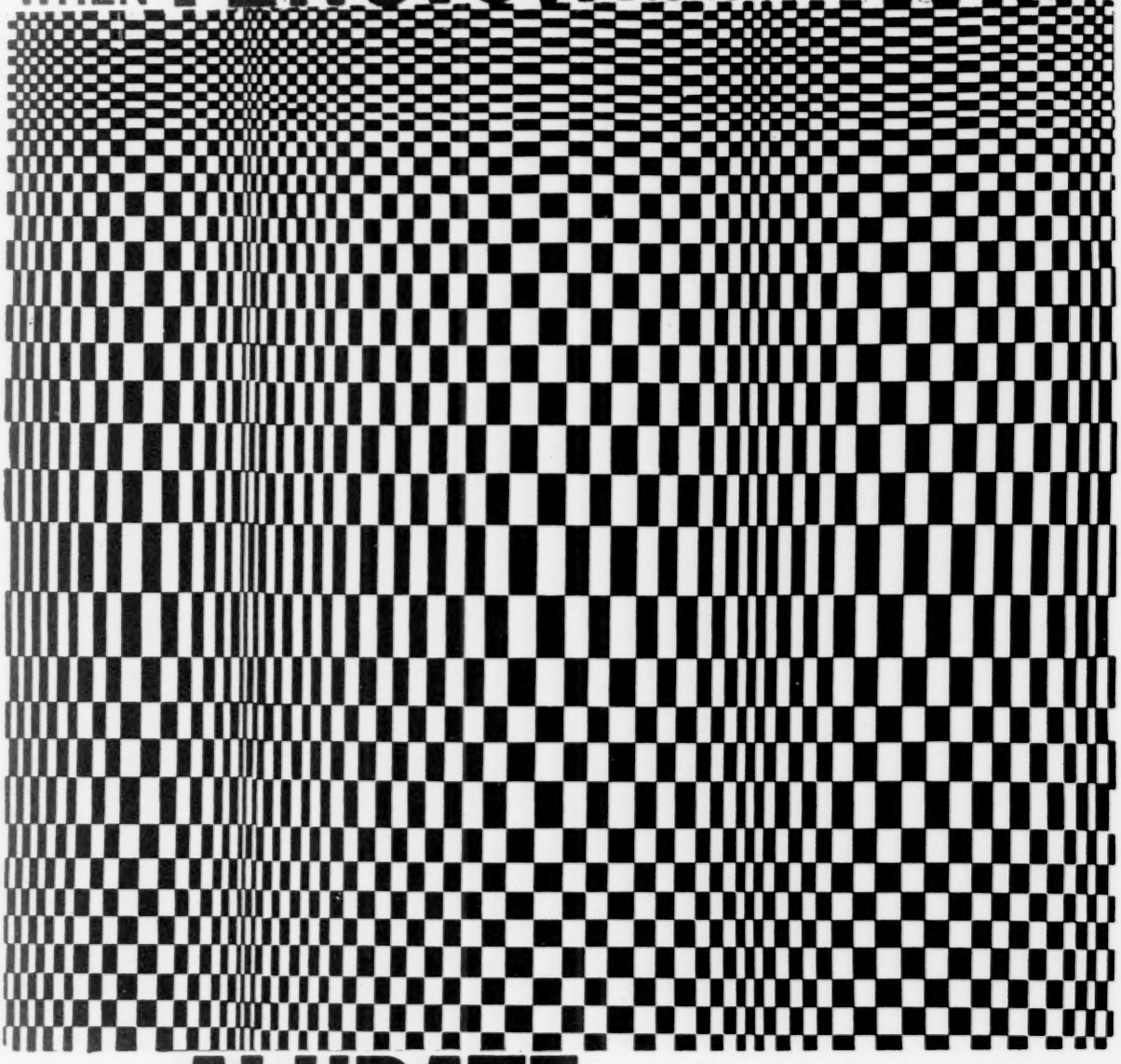
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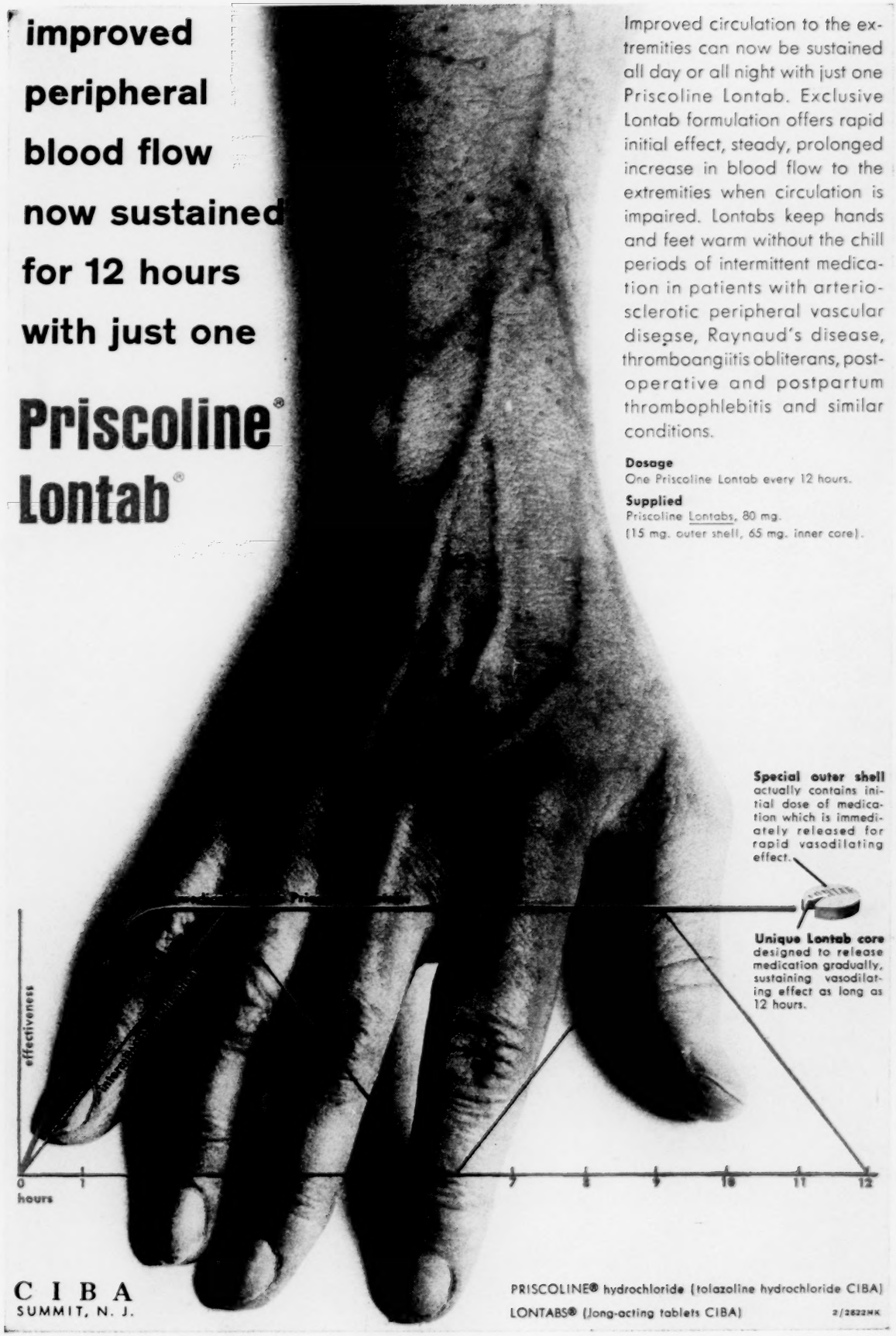
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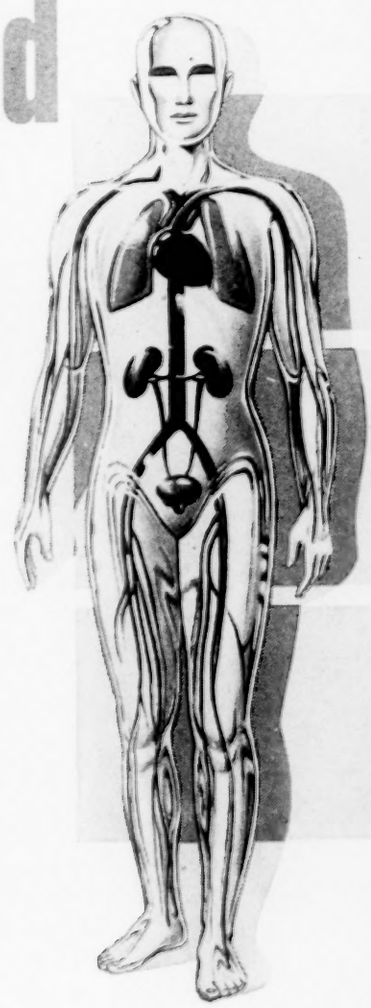
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■ Add or adjust other agents as required: HYDRODIURIL enhances the activity of all commonly-used antihypertensive agents; thus, the dosage of other medication (rauwolfia, reserpine, hydralazine, veratrum) should be initiated or adjusted as indicated by patient condition. If a ganglion-blocking agent is contemplated or being used, usual dosage must be reduced by 50 per cent.

■ Adjust dosage of all medication: the patient must be frequently observed and careful adjustment of all agents should be made to establish optimal maintenance dosage.

Supplied: 25 mg. and 50 mg. scored tablets HYDRODIURIL (Hydrochlorothiazide) bottles of 100 and 1,000.
Additional literature for the physician is available on request.

HYDRODIURIL is a trademark of Merck & Co., Inc. Trademarks outside the U. S.: DICHLOTRIDE, DICLOTRIDE, HYDROSALURIC.

MSD MERCK SHARP & DOHME, Division of Merck & Co., Inc., Philadelphia 1, Pa.

Tofrānil® a thymoleptic

brand of imipramine HCl

Specific in Depression

does

Produce remission or improvement in 70-85% of cases

Act effectively in all types of depression

Afford equally good results in severe as in mild cases

Achieve therapeutic benefit with minimal risk of serious side reaction

Indications for Tofrānil include:

Endogenous Depression, Reactive Depression, Involutional Melancholia, Senile Depression, Depression associated with other Psychiatric Disorders.

Availability: Tofrānil (brand of imipramine HCl) tablets of 25 mg. bottles of 100. Ampuls of 25 mg. (for intramuscular administration only) cartons of 10 and 50.

.....not a MAO inhibitor

does not

Inhibit monoamine oxidase either in brain or liver with its associated risks

Produce dangerous potentiation of other drugs such as barbiturates and alcohol

Act by producing undesirable central nervous stimulation leading to agitation and excitement

Cause disturbance of color vision

The efficacy of Tofranil is attested by more than 50 published reports and confirmed by clinical experience in more than 50,000 cases.

Detailed Literature Available on Request.

Geigy, Ardsley, New York

Geigy

Unquestioned therapeutically

...long established clinically

TRISEM

SUSPENSION (chocolate-flavored)

For the many bacterial infections that respond promptly to triple sulfonamide therapy, Trisem presents a preferred formula.

Each 5 cc. contains, in a pleasant, chocolate-flavored vehicle:

Sulfamerazine (microcrystalline)	0.167 Gm. (2 3/5 gr.)
Sulfadiazine (microcrystalline)	0.167 Gm. (2 3/5 gr.)
Sulfamethazine (microcrystalline)	0.167 Gm. (2 3/5 gr.)

Each 5 cc. (1 tsp.) provides 0.5 Gm. total sulfonamides.

Each 15 cc. (1 tbsp.) provides 1.5 Gm. total sulfonamides.

ADVANTAGES

- **wide patient acceptability**
- **unquestioned therapeutic value**
- **high index of safety**
- **broad antibacterial spectrum**
- **provides high blood levels promptly**
- **economical for the patient**

Many physicians prefer to use the sulfonamides to control bacterial infections because resistant organisms rarely develop. Nor, as with some broad spectrum therapy, is there the complication of such after-effects as moniliasis.

PACKAGING: In pint and gallon bottles.

THE S. E. MASSENGILL COMPANY

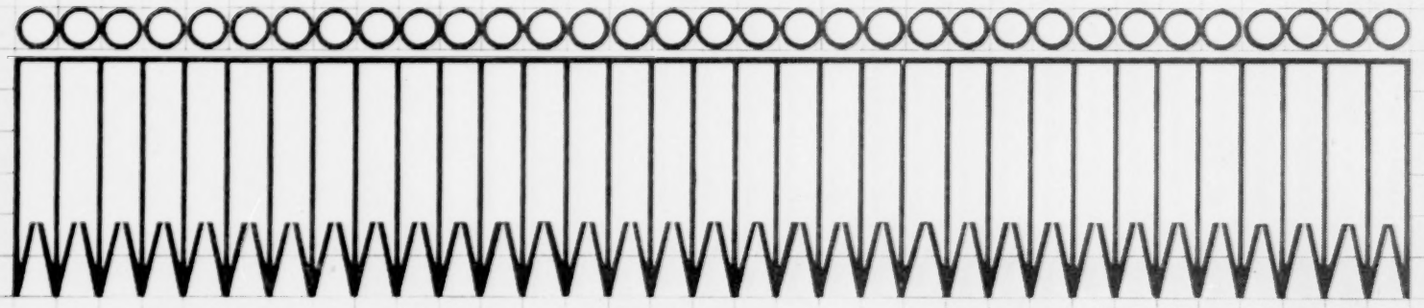
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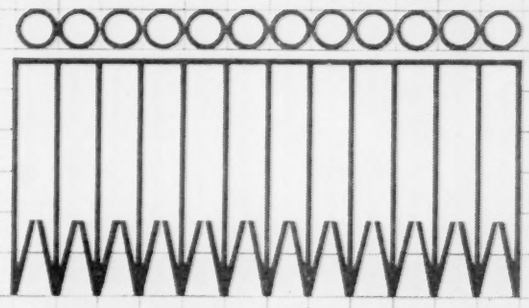
Decadron®

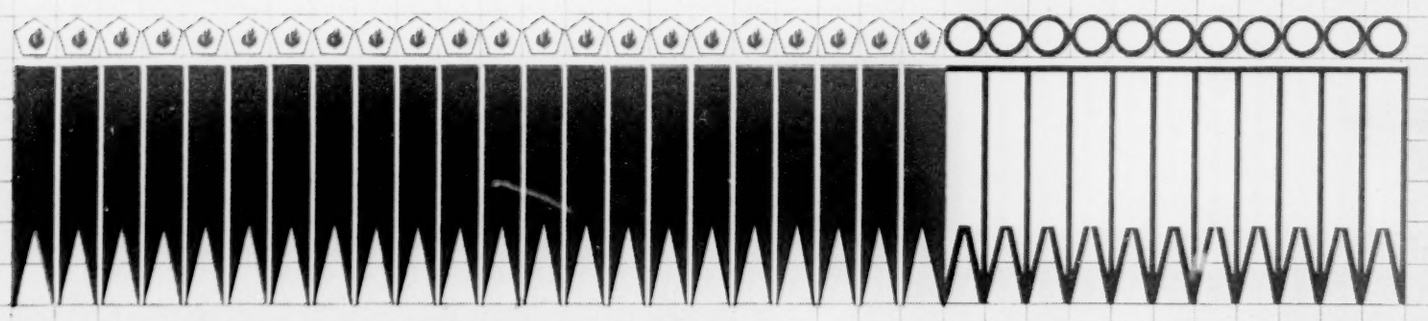
DEXAMETHASONE

treats more patients more effectively...

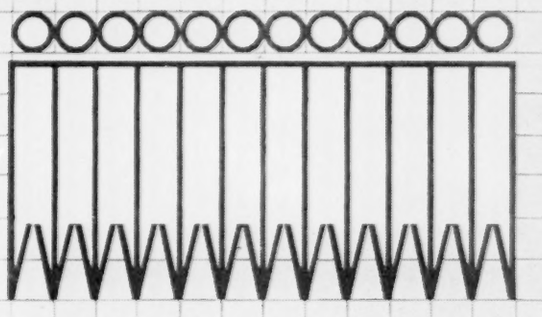


Of 45 arthritic patients
who were refractory
to other corticosteroids*





22 were successfully
treated with **Decadron**[1,2]



1. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.
2. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.

*Cortisone, prednisone and prednisolone.

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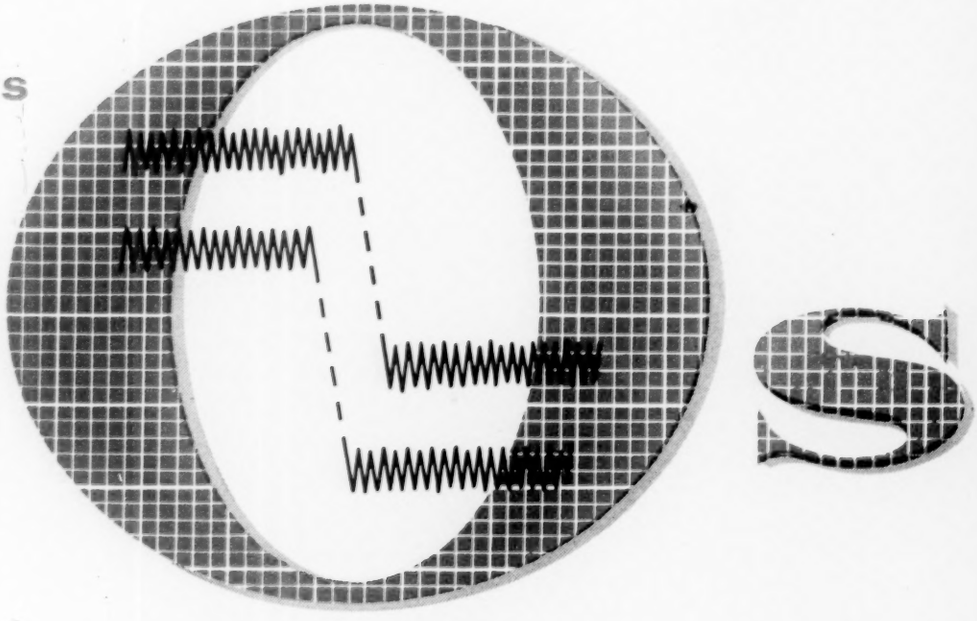
Additional information on DECADRON is available to physicians on request.

Merck Sharp & Dohme
DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

announcing

the keystone in a new and effective antihypertensive regimen

TABLETS



OSTENSIN is the registered trademark for Trimethidinium Methosulfate, Wyeth.

outstanding advantages of an improved antihypertensive regimen . . . easier management, greater patient comfort, improved clinical picture

OSTENSIN, used with chlorothiazide or its derivatives, provides a superior new antihypertensive regimen[1,2,3,4] with reduced dosage, by-effects decreased, and maximal clinical benefits.

The sympathetic blockade produced with OSTENSIN lowers systolic and diastolic blood pressure with predictable effectiveness and yet—because of minimal parasympathetic action—with fewer and less severe by-effects.[1,2,3]

Clinical experience[1,2,3] shows that such by-effects as constipation, postural hypotension, and genitourinary disturbances are less frequent and less severe with OSTENSIN than with other ganglionic-blocking compounds. No psychotic reactions, mental depression, or such neural disorders as tremors have been reported with OSTENSIN.

OSTENSIN offers further advantages in oral administration, low dosage, smooth and prolonged antihypertensive action, prompt onset, no evidence of inherent toxicity, and rare drug tolerance.[3]

OSTENSIN is indicated in diastolic hypertension. (Diastolic hypertension is defined as ". . . the elevation of diastolic blood pressure to 90 mm. Hg or above."[5])

PLEASE TURN PAGE

tensin®

Ganglionic blockade with fewer and milder by-effects

Wyeth®
Philadelphia 1, Pa.

. . . documented improvement in antihypertensive management

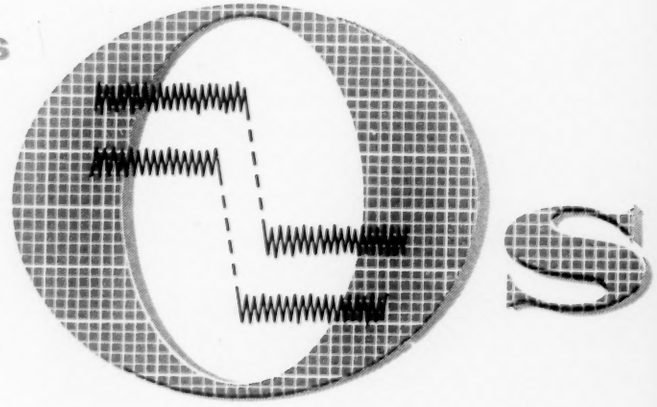
in blood-pressure control
in by-effect control

"Of particular interest has been the virtual absence of constipation despite adequate blood pressure control. This finding suggests a lower risk of paralytic ileus. . . ."[1]

BY-EFFECTS OF THREE OTHER GANGLIONIC-BLOCKING AGENTS[6,7,8] COMPARED WITH THOSE OF OSTENSIN[1,9]

	Other Agents	OSTENSIN
Constipation	59-69% of patients	5% of patients
Postural hypotension	33-59% of patients	37% of patients
Visual disturbances	42-50% of patients	34% of patients
Dry mouth	38-41% of patients	15% of patients

TABLETS



1. Dunsmore, R.A., et al.: Am. J. M. Sc. *236*:483 (Oct.) 1958. 2. Blaquier, P., et al.: Univ. Michigan M. Bull. *24*:409 (Oct.) 1958. 3. Smirk, F.H.: Submitted for publication. 4. Janney, J.F.: Submitted for publication. 5. Council on Drugs, A.M.A.: J.A.M.A. *166*:640 (Feb. 8) 1958. 6. Freis, E.D., and Wilson, I.M.: Circulation *13*:856 (June) 1956. 7. Moyer, J.H., et al.: A.M.A. Arch. Int. Med. *98*:187 (Aug.) 1956. 8. Moyer, J.H., et al.: Am. Pract. & Dig. Treat. 7:1765 (Nov.) 1956. 9. Dunsmore, R.A. In Tislow, R.F., et al.: Scientific Exhibit. Presented at Annual Convention of A.M.A., San Francisco, June 23-27, 1958.

. . . technique of management

Dosage: Dosage is individualized. Therapy is initiated with one 20-mg. tablet *before* breakfast, in midafternoon, and before retiring, or at approximately 8-hour intervals. When OSTENSIN is required only twice daily, it should be administered *before* breakfast and *before* the evening meal.

Chlorothiazide or its derivatives: To increase sodium chloride excretion and enhance hypotensive activity, chlorothiazide or one of its derivatives should be administered with the morning and midafternoon doses of OSTENSIN. Some patients may require only the morning dose of the diuretic.

Adjustment of dosage: Dosage is adjusted according to blood-pressure readings with the patient standing. Each dose of OSTENSIN is increased by 20 mg. every third day, until a satisfactory response is obtained. Care should be taken to avoid episodes of postural hypotension. The total daily dose is usually in a range of from 40 to 300 mg. Most patients require approximately 120 to 140 mg. daily, divided into three appropriate doses.

Alternate method: OSTENSIN therapy alone may be initiated and the dose adjusted as explained above. If, in these patients, it becomes desirable to add chlorothiazide or one of its derivatives to the regimen, the daily dose of OSTENSIN should be reduced by half and, if necessary, increased until an effective dosage schedule is obtained.

Pharmacologic by-effects: The incidence and severity of pharmacologic by-effects are greatly reduced with the OSTENSIN regimen and do not parallel the degree of hypotensive effect. In most instances, symptoms may be troublesome only in the early stages of treatment and will disappear or diminish as therapy progresses. Nevertheless, the patient should be cautioned that they may occur—blurring of vision, postural hypotension, constipation, dry mouth, decreased libido and delay in orgasm in young males. (Consult the package circular for management.)

Caution: OSTENSIN should be administered with caution to patients with severe renal disease. In those patients with increasing blood urea nitrogen, OSTENSIN should be discontinued.

Contraindications: Organic pyloric stenosis, marked cerebral arteriosclerosis, recent coronary thrombosis, recent cerebral thrombosis, bleeding peptic ulcer.

Supplied: Tablets, scored, 20 and 40 mg., vials of 100.

COMPREHENSIVE LITERATURE SUPPLIED ON REQUEST

tensin®

Ganglionic blockade with fewer and milder by-effects

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NEW concept
in chronic constipation . . .
and especially that associated with the irritable bowel syndrome



DECHOTYL
TRABLETS*

provides physiologic support until function returns

*T.M. for AMES trapezoid-shaped tablet.



DECHOTYL™

TRABLETS*

safe, gentle transition to normal bowel function

DECHOTYL provides gentle stimulation of the bowel and helps restore normal consistency of the intestinal contents to gradually re-establish normal bowel function in your chronically constipated patients.

THE RATIONALE of DECHOTYL is based on an effective combination of therapeutic agents:

DECHOLIN®, dehydrocholic acid, AMES, (200 mg.), the most potent hydrocholeretic available, is a chemically pure bile acid and has been used effectively in the treatment of biliary tract disorders for many years. It produces an increased flow of thin bile which helps to lower surface tension of intestinal fluids, promotes emulsification and absorption of fats and mildly stimulates intestinal peristalsis.

Desoxycholic Acid (50 mg.)—a choleretic, also is a chemically pure bile acid and stimulates an increased flow of bile, lowers surface tension and stimulates peristalsis. By emulsifying fat globules, desoxycholic acid aids the digestive action of the fat-splitting enzyme, lipase. DECHOLIN and desoxycholic acid thus favorably influence the constitution and the movement of the intestinal contents.

Dioctyl Sodium Sulfosuccinate (50 mg.) is a wetting agent which lowers surface tension and aids the penetration of intestinal fluids into the fecal mass, providing a moist stool of normal consistency.

EFFECTIVE: Bile influences the constitution as well as the movement of the intestinal contents. The ingredients of major importance are DECHOLIN and desoxycholic acid which increase the flow of bile, lower surface tension, promote emulsification and absorption of fats and mildly stimulate intestinal peristalsis. With dioctyl sodium sulfosuccinate, a good therapeutic effect can be obtained without the danger of toxicity or decreasing effectiveness even when used regularly.

SAFE: Clinical evidence indicates that the constituents of DECHOTYL cause no systemic sensitivity, drug accumulation, habituation or interference with nutrition. Orally, in therapeutic amounts, DECHOTYL is without significant toxic effect. The only side effect following oral administration is diarrhea if the dosage is excessive.

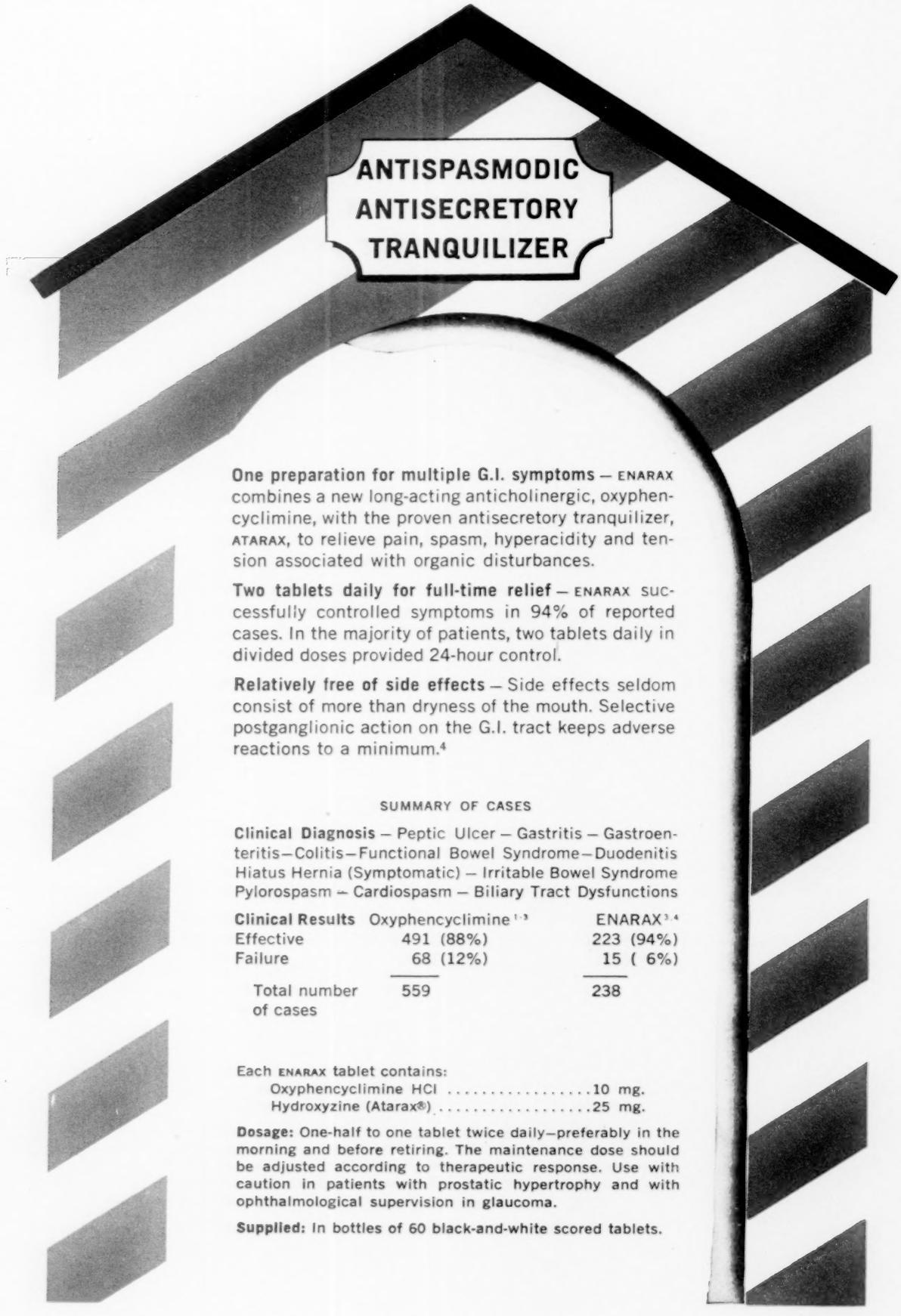
Dosage: *Average adult dose*—TWO TRABLETS* at bedtime. Some individuals initially may require 1 to 2 TRABLETS three or four times daily. *Contraindications:* Biliary tract obstruction; acute hepatitis.

Available: TRABLETS,* coated, yellow, trapezoid-shaped; bottles of 100.

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One preparation for multiple G.I. symptoms — ENARAX combines a new long-acting anticholinergic, oxyphencyclimine, with the proven antisecretory tranquilizer, ATARAX, to relieve pain, spasm, hyperacidity and tension associated with organic disturbances.

Two tablets daily for full-time relief — ENARAX successfully controlled symptoms in 94% of reported cases. In the majority of patients, two tablets daily in divided doses provided 24-hour control.

Relatively free of side effects — Side effects seldom consist of more than dryness of the mouth. Selective postganglionic action on the G.I. tract keeps adverse reactions to a minimum.[4]

SUMMARY OF CASES

Clinical Diagnosis — Peptic Ulcer — Gastritis — Gastroenteritis—Colitis—Functional Bowel Syndrome—Duodenitis Hiatus Hernia (Symptomatic) — Irritable Bowel Syndrome Pylorospasm — Cardiospasm — Biliary Tract Dysfunctions

Clinical Results	Oxyphencyclimine[1-3]	ENARAX[3,4]
Effective	491 (88%)	223 (94%)
Failure	68 (12%)	15 (6%)
Total number of cases	559	238

Each ENARAX tablet contains:
Oxyphencyclimine HCl .....10 mg.
Hydroxyzine (Atarax®) .....25 mg.

Dosage: One-half to one tablet twice daily—preferably in the morning and before retiring. The maintenance dose should be adjusted according to therapeutic response. Use with caution in patients with prostatic hypertrophy and with ophthalmological supervision in glaucoma.

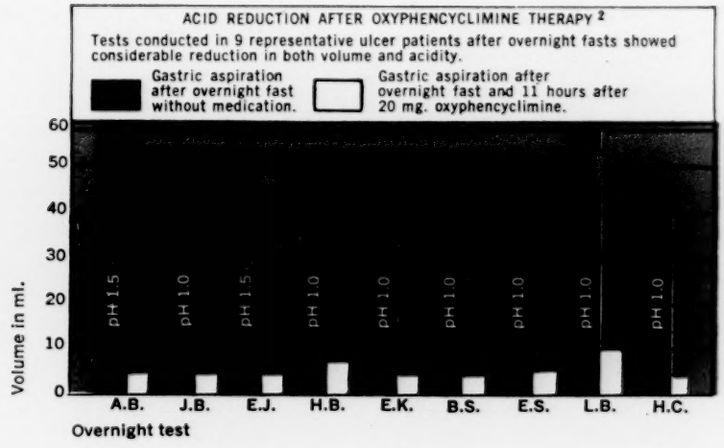
Supplied: In bottles of 60 black-and-white scored tablets.



ENARAX®

(oxyphencyclimine plus ATARAX®)

A SENTRY FOR THE G.I. TRACT



References: 1. Steigmann, F.: Study conducted at Cook County Hospital, Chicago, Illinois: In press. 2. Winkelstein, A.: Am. J. Gastroenterol. **32**:66 (July) 1959. 3. Data in Roerig Medical Department files. 4. Leming, B. H., Jr.: Clin. Med. **6**:423 (Mar.) 1959.

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In prophylaxis of angina pectoris

"The best results . . ."

"The best results . . . in both clinical and electrocardiographic response, were observed with a combination of meprobamate and pentaerythritol tetranitrate [EQUANITRATE]. . . ." Russek[1] so reported using double-blind methods in an important new study of pentaerythritol tetranitrate, a placebo, meprobamate, and EQUANITRATE.

EQUANITRATE reduces the frequency and severity of attacks and controls angina-triggering emotions.

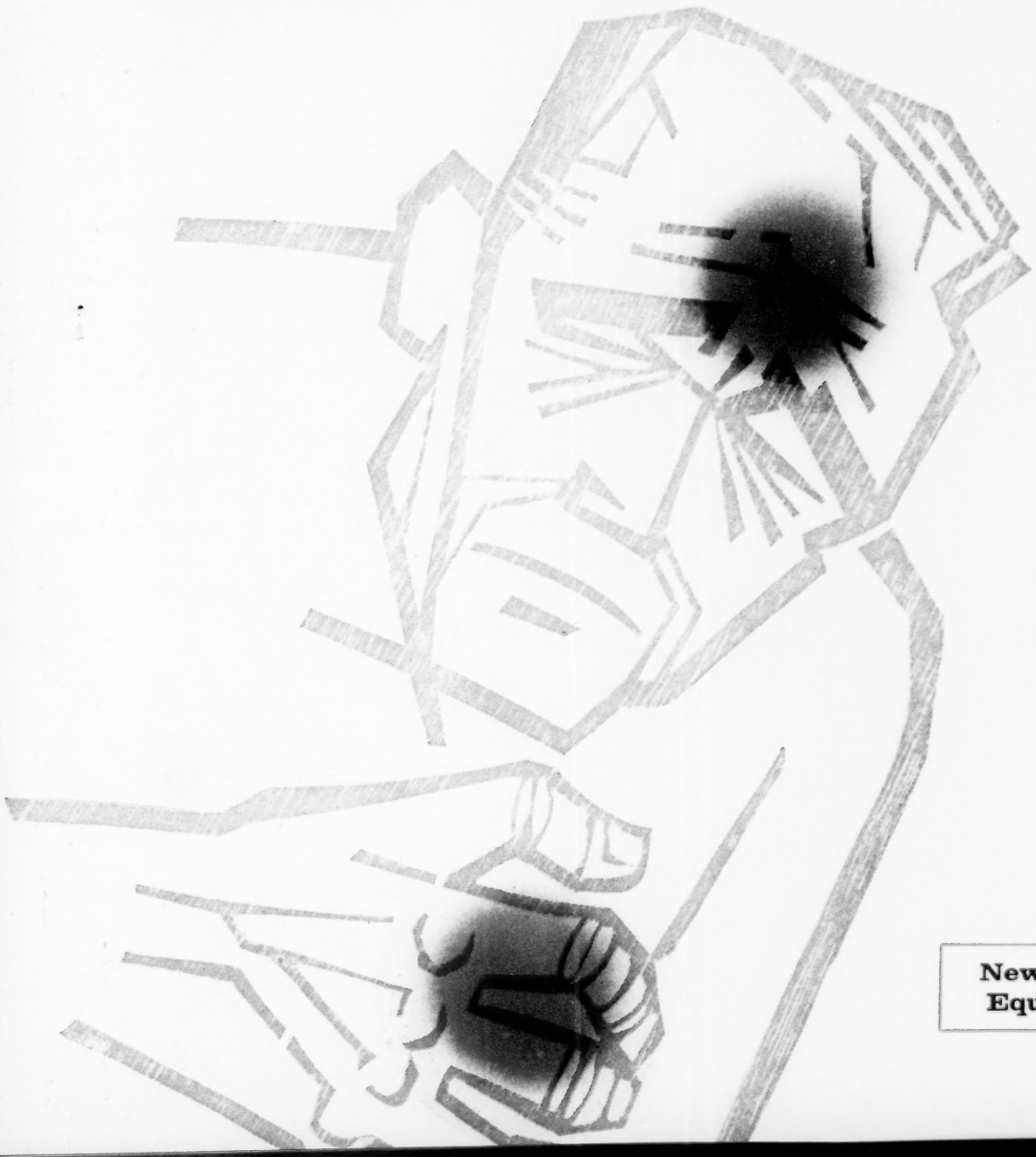
Supplied: EQUANITRATE **10** (200 mg. meprobamate, 10 mg. pentaerythritol tetranitrate), white oval tablets, vials of 50. EQUANITRATE **20** (200 mg. meprobamate, 20 mg. pentaerythritol tetranitrate), yellow oval tablets, vials of 50.

1. Russek, H.I.: Am. J. Cardiol. *3*:547 (April) 1959.

Equanitrate*

Meprobamate and Pentaerythritol Tetranitrate, Wyeth

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Newly Available
Equanitrate 20

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HOMOGENIZATION makes the difference



Microphotograph of a **HOMAGENET**

Microphotograph of usual vitamin product

The photographs above point out the difference between Homagenets and many vitamin products. By means of the homogenization process, both oil and water soluble vitamins are presented in microscopic particles. Due to the fine particle size, there is much greater surface exposure, which permits quicker absorption and better utilization. This has been clinically proved by Lewis and others.[1]

1. Lewis, J.M., et al.: J. Pediatrics, *31*:496

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HOMAGENETS*

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in solid form

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HOMAGENETS are available in five formulas:

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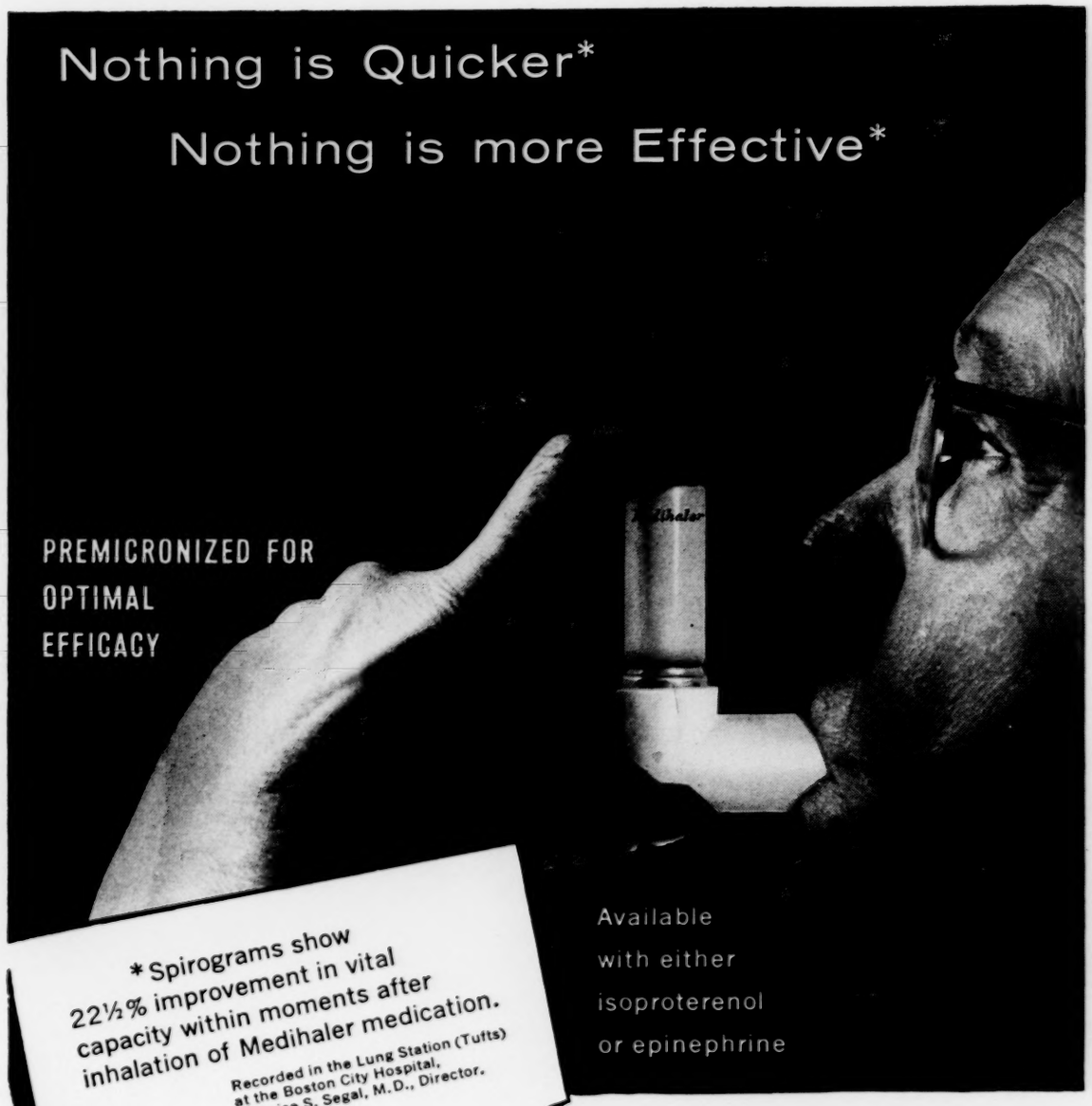
*U.S. Pat. 2676136. Other Pat. Pending

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Available with either isoproterenol or epinephrine

Automatically measured-dose aerosol medications.
Nonbreakable...Shatterproof
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Medihaler-ISO® Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.06 mg. isoproterenol.

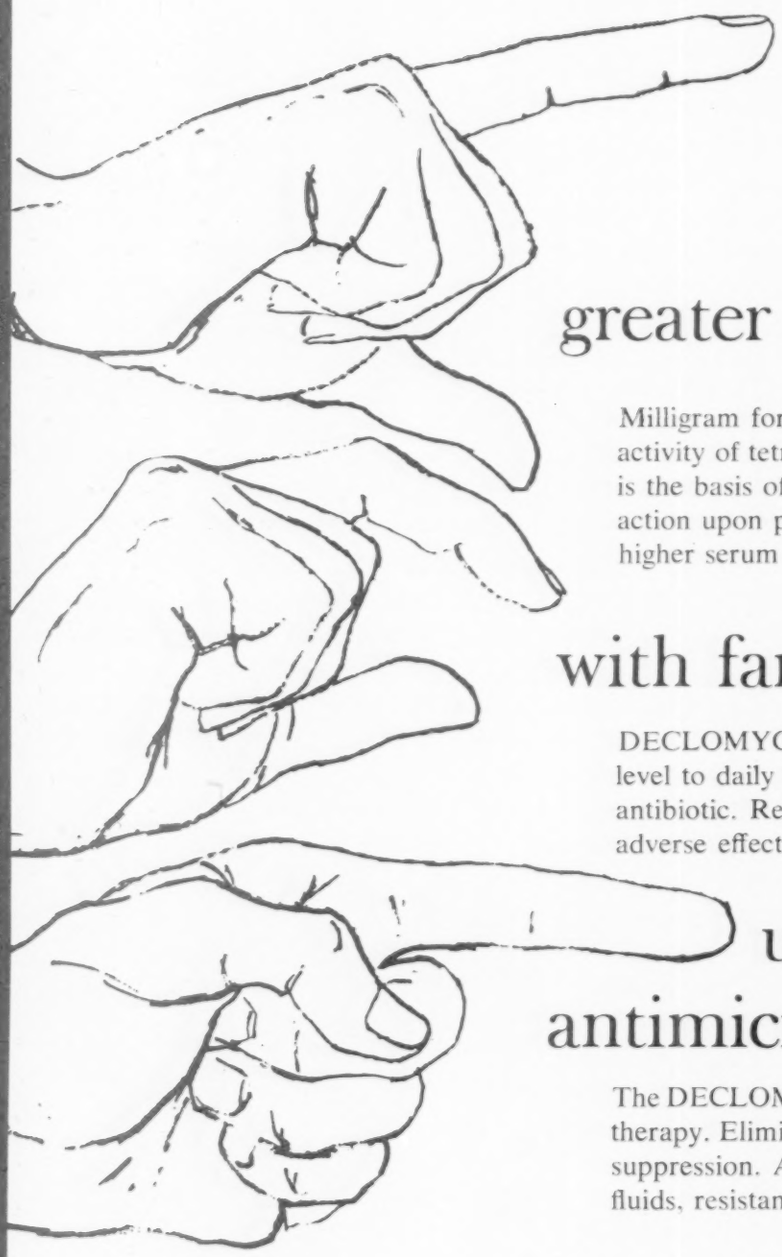
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with far less antibiotic intake

DECLOMYCIN demonstrates the highest ratio of prolonged activity level to daily milligram intake of any known broad-spectrum antibiotic. Reduction of antibiotic intake reduces likelihood of adverse effect on intestinal mucosa or interaction with contents.

unrelenting peak antimicrobial attack

The DECLOMYCIN high activity level is uniquely constant throughout therapy. Eliminates peak-and-valley fluctuation, favoring continuous suppression. Achieved through remarkably greater stability in body fluids, resistance to degradation and a low rate of renal clearance.

*Hirsch, H. A., and Finland, M.: *New England J. Med.* 260:1099 (May 28) 1959.

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Demethylchlortetracycline Lederle

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plus
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DECLOMYCIN maintains activity for one to two days after discontinuance of dosage. Features unusual security against resurgence of primary infection or secondary bacterial invasion—two factors often resembling a "resistance problem"—enhancing the traditional advantages of tetracycline . . . for greater physician-patient benefit

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DECLOMYCIN Capsules, 150 mg., bottles of 16 and 100. Adult dosage: 1 capsule four times daily.

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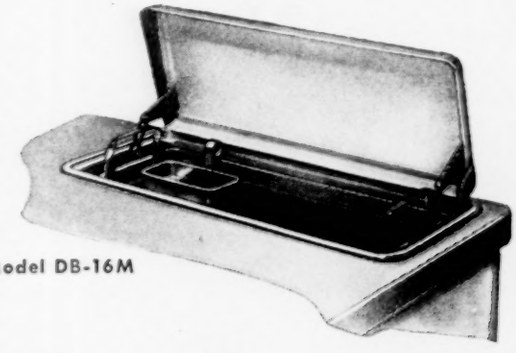
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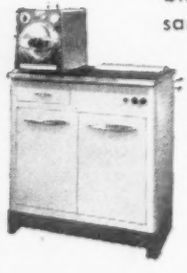


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Amsco's large Office Pressure-Steam Sterilizer, 613-R Dynaclave, or 8" Square Autoclave, Cat. No. 8816, can be conveniently located on work counter of the double cabinet.

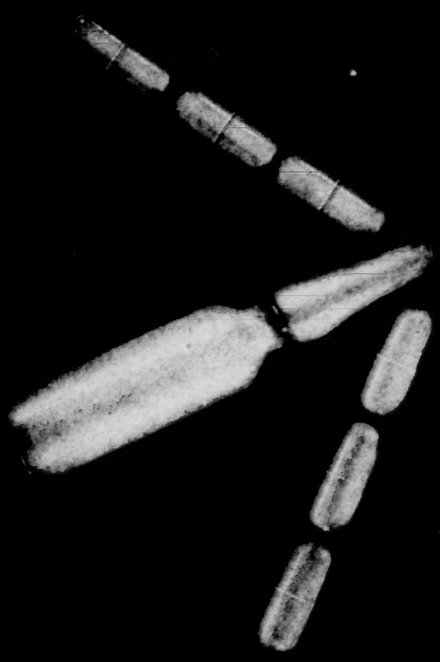
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INTRAMUSCULAR SOLUTION

Initiation of therapy in **minutes after diagnosis** with new, ready-to-inject Terramycin Intramuscular Solution provides maximum, sustained absorption of potent broad-spectrum activity.

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oxytetracycline with glucosamine

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Continuation with oral Cosa-Terramycin every six hours will provide highly effective antibacterial serum and tissue levels for prompt infection control.

The unsurpassed record of clinical effectiveness and safety established for Terramycin is your guide to successful antibiotic therapy.

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100 mg./2 cc. ampules 250 mg./2 cc. ampules

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125 mg. and 250 mg.

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■ Exhibits unusual analgesic properties, different from those of any other drug ■ Specific and superior in relief of SOMAtic pain

■ Modifies central perception of pain without abolishing natural defense reflexes ■ Relaxes abnormal tension of skeletal muscle

SOMA™

N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

■ More specific than salicylates ■ Less drastic than steroids

■ More effective than muscle relaxants

SOMA has an unique analgesic action. It apparently modifies central pain perception without abolishing peripheral pain reflexes. SOMA is particularly effective in relieving joint pain. Patients say that they feel better and sleep better with SOMA than with any previously used analgesic, sedative or relaxant drug.
SOMA also relaxes muscle hypertonia, with its stresses on related joints, ligaments and skeletal structures.

ACTS FAST. Pain-relieving and relaxant effects start in 30 minutes and last 6 hours.

NOTABLY SAFE. Toxicity of SOMA is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy on high dosage.

EASY TO USE. Usual adult dose is one 350 mg. tablet 3 times daily and at bedtime.

SUPPLIED: Bottles of 50 white sugar-coated 350 mg. tablets.
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Car: stalled

Temper: mild

Ulcer: quiet

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His physician, aware that *the patient as well as the ulcer* must be treated, has prescribed ALUDROX SA.

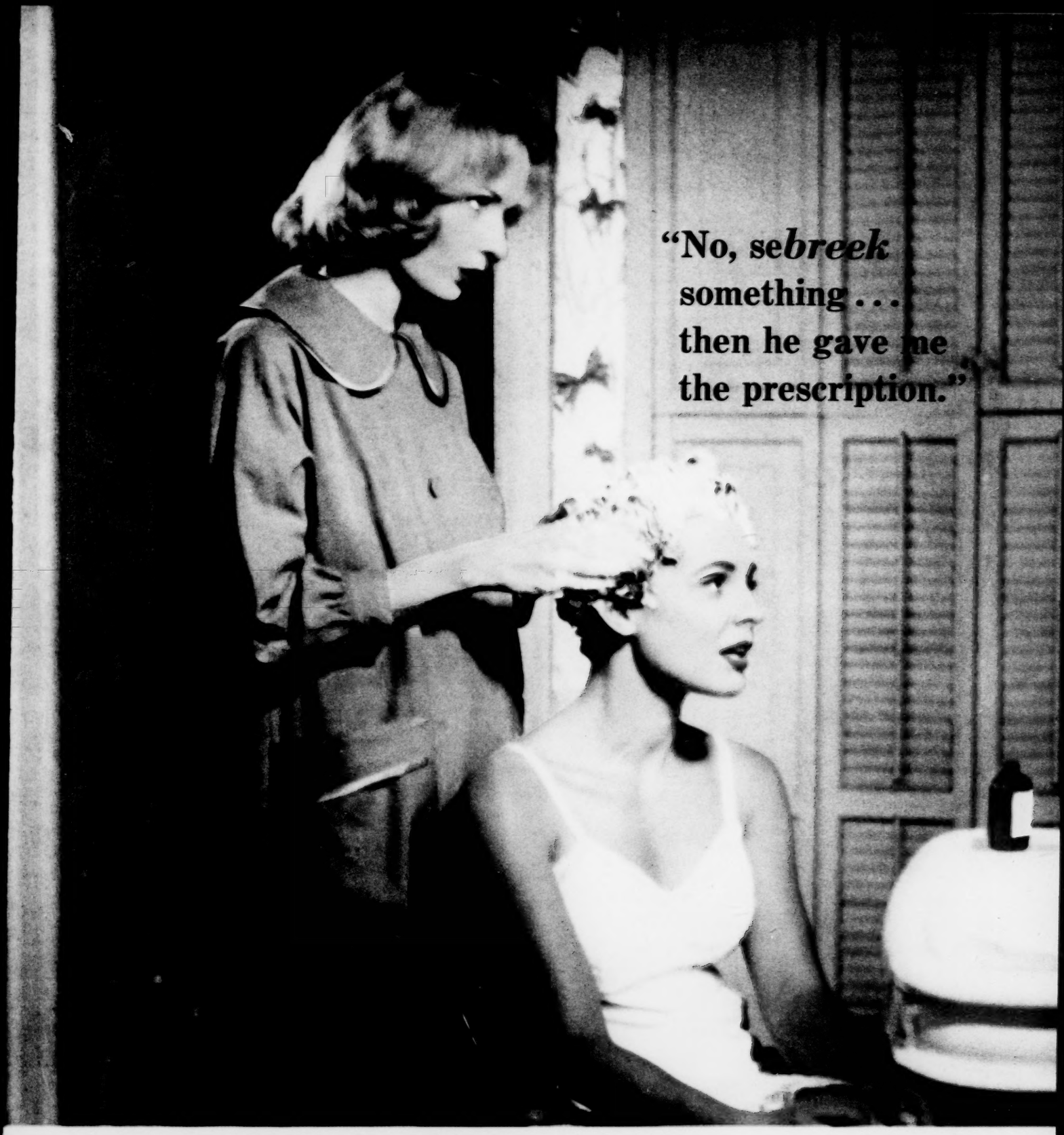
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Dermatitis, dear. **Seborrheic Dermatitis.** Now you know what dandruff really is. Good thing you mentioned it to your doctor. Most people plug along, trying everything in sight—lotions, tonics, pastes, shampoos, the works. They ought to know dandruff is a *medical* problem, needs a *medical* answer. Watch for the all too familiar signs, doctor. Your patients will appreciate the tip—and the prescription.

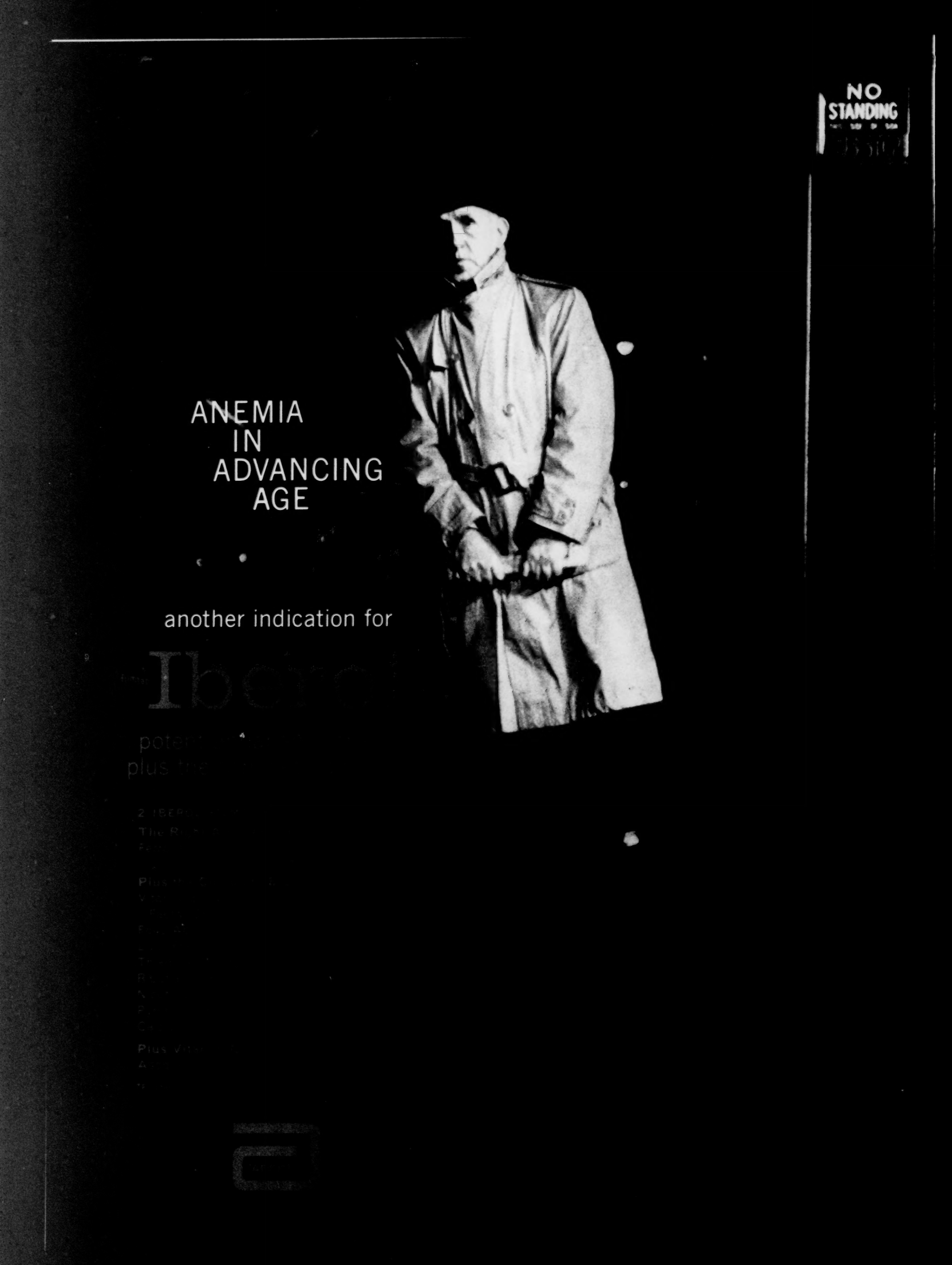
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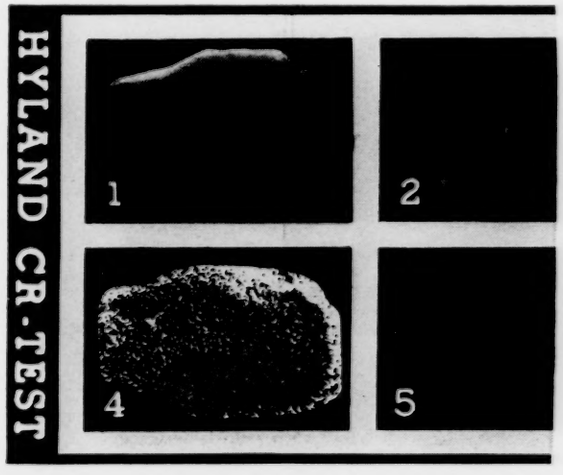
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Levels of C-reactive protein are equally easy to determine. Prepare serum dilutions of test specimen in buffered diluent. On successive sections of glass slide, mix one drop of CR-TEST reagent with one drop of each serum dilution. The highest dilution showing visible flocculation within two minutes is taken as the C-reactive protein titer of the specimen.

SUPPLIED

Kits containing Latex-Anti-C-Reactive Protein Reagent, Glycine-Saline Buffer Diluent for serum dilution, capillary pipettes for serum transfer, and 2 divided glass slides. Each kit sufficient for 60 screening tests. $10.00 per kit.

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the new alternative:

In 25 years, the antibacterials have progressed from the status of heroic therapy to "universal" medication. This has brought into focus certain unexpected problems relating both to bacterial and to host response.

Shifts in bacterial flora—particularly of the gastrointestinal, as well as the respiratory and urinary tracts—pose entirely new therapeutic problems. The emergence of resistant strains of bacteria creates still another hazard. Also, anaphylactic reactions often hamper critically needed therapy.

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*Some infections due to antibiotic-resistant strains have responded to Madribon.

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1. W. P. Boger, *Antibiotics Annual 1958-1959*, New York, Medical Encyclopedia, Inc., 1959, p. 48. 2. B. A. Koechlin, W. Kern and R. Engelberg, *Antibiotic Med. & Clin. Therapy*, 6:(Suppl. 1), 22-31, Feb. 1959. 3. S. Ross, J. R. Puig and E. A. Zaremba, *Antibiotics Annual 1958-1959*, New York, Medical Encyclopedia, Inc., 1959, p. 56. 4. E. H. Townsend, Jr. and A. Borgstedt, *Antibiotics Annual 1958-1959*, New York, Medical Encyclopedia, Inc., 1959, p. 64. 5. J. D. Young, Jr., W. S. Kiser and O. C. Beyer, *Antibiotic Med. & Clin. Therapy*, 6:(Suppl. 1), 53-56, Feb. 1959. 6. B. H. Leming, Jr., C. Flanigan, Jr. and B. R. Jennings, *Antibiotic Med. & Clin. Therapy*, 6:(Suppl. 1), 32-39, Feb. 1959. 7. T. D. Michael, *Antibiotic Med. & Clin. Therapy*, 6:(Suppl. 1), 57-60, Feb. 1959. 8. W. A. Leff, *Antibiotic Med. & Clin. Therapy*, 6:(Suppl. 1), 44-48, Feb. 1959. 9. J. C. Elia, *Antibiotic Med. & Clin. Therapy*, 6:(Suppl. 1), 61-64, Feb. 1959. 10. M. J. Mosely, Jr., *J. Nat. M. A.*, 51:258, July 1959. 11. S. Guss and A. J. Spiro, *Pediatric Conferences*, 2:14, Mar. 1959. 12. H. P. Ironson and C. Patel, *Antibiotic Med. & Clin. Therapy*, 6:(Suppl. 1), 40-43, Feb. 1959. 13. R. J. Schnitzer and W. F. DeLorenzo, *Antibiotic Med. & Clin. Therapy*, 6:(Suppl. 1), 17-21, Feb. 1959. 14. R. J. Schnitzer, W. F. DeLorenzo, E. Grunberg and R. Russomanno, *Proc. Soc. Exper. Biol. & Med.*, 99:421, Nov. 1958. 15. W. F. DeLorenzo and R. Russomanno, *Antibiotic Med. & Clin. Therapy*, 6:(Suppl. 1), 14-16, Feb. 1959. 16. B. Fust and E. Bochni, *Antibiotic Med. & Clin. Therapy*, 6:(Suppl. 1), 3-10, Feb. 1959. 17. W. F. DeLorenzo and A. M. Schumacher, *Antibiotic Med. & Clin. Therapy*, 6:(Suppl. 1), 11-13, Feb. 1959. 18. O. Brandman, C. Oyer and R. Engelberg, *J. M. Soc. New Jersey*, 56:24, Jan. 1959. 19. J. F. Glenn, J. R. Johnson and J. H. Semans, *Antibiotic Med. & Clin. Therapy*, 6:(Suppl. 1), 49-52, Feb. 1959. 20. L. O. Randall, R. E. Bagdon and R. Engelberg, *Toxicol. & Appl. Pharmacol.*, 1:28, Jan. 1959. 21. S. M. Finegold, Z. Kudinoff, H. O. Kendall and V. E. Kvinge, *Ann. New York Acad. Sc.*, 82(1):44-50, 1959. 22. W. J. Grace, *ibid.*, p. 51. 23. L. E. Skinner, *ibid.*, pp. 57-60. 24. C. W. Daeschner, *ibid.*, pp. 64-70. 25. S. W. Levy, *ibid.*, pp. 80-83. 26. M. M. Cahn and E. J. Levy, *ibid.*, pp. 84-91. 27. M. Sierp and J. W. Draper, *ibid.*, pp. 92-104. 28. G. A. Moore, *ibid.*, pp. 61-63. 29. W. P. Boger and J. J. Gavin, *ibid.*, pp. 18-30. 30. J. C. Elia, *ibid.*, pp. 52-56. 31. W. S. Kiser, O. C. Beyer and J. D. Young, *ibid.*, pp. 105-113. 32. B. H. Leming, Jr. and C. Flanigan, Jr., *ibid.*, pp. 31-39. 33. R. E. Bagdon, L. O. Randall and W. A. Leff, *ibid.*, pp. 3-9. 34. W. F. DeLorenzo and R. J. Schnitzer, *ibid.*, pp. 10-17. 35. G. Carroll in W. S. Kiser, *et al.*, *ibid.*, pp. 110-113. 36. S. Krugman in E. H. Townsend, Jr. and A. Borgstedt, *ibid.*, pp. 78-79. 37. E. H. Townsend, Jr. and A. Borgstedt, *ibid.*, pp. 71-79. 38. T. D. Michael, *ibid.*, pp. 40-43. 39. A. Thill, to be published.

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pre-eminently effective whenever diuresis is desired

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RECORD OF TREATMENT (At a leading New York City hospital. Photos used with permission of the patient.)

Date	3/3	3/4	3/5	3/6	3/7	3/8	3/9	3/10	3/11	3/12	3/13	3/14	3/15	3/16	3/17	3/18	3/19	3/20	3/21	3/22	3/23
Weight (pounds)	178	176	170	169	167	159	158	158	157	153	155	155	156	154	153	154	153	—	—	151	149
Rx	M*	Esidrix 50 mg. b.i.d.																			

*Mercurial diuretic



After 19 Days on Esidrix:
Weight 149 lbs.

H. K., 44 years old, with history of heavy drinking. Previously hospitalized in 1954, with diagnosis of Laennec's cirrhosis. Admitted on 3/3/59, patient complained of swollen abdomen, swelling in both legs and exertional dyspnea.

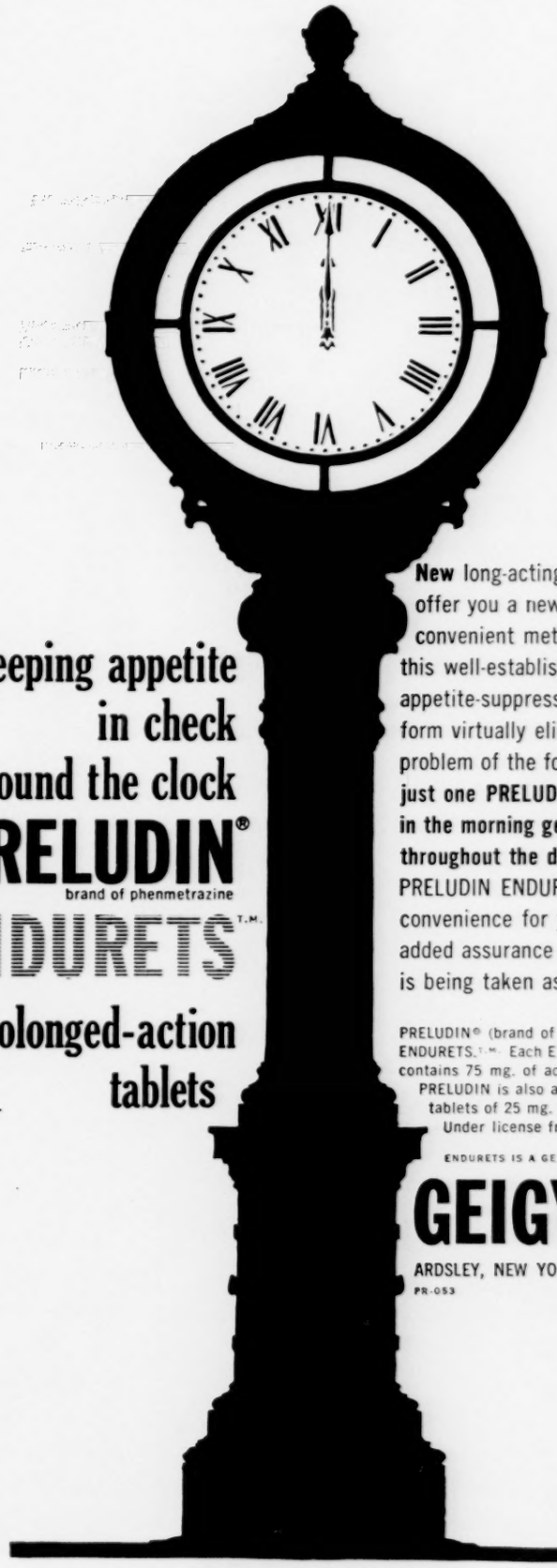
Findings: Abdomen enlarged in girth with definite fluid wave; liver palpated 4 fingerbreadths below the costal margin; pedal edema (4+). Patient not in acute distress. Blood pressure, 140/80 mm. Hg; pulse, 112/min.; respiration, 20/min.

Treatment: Mercurial diuretic on 3/3 and 3/4, followed by Esidrix, 50 mg. b.i.d., from 3/5 to 3/23 when patient signed out of hospital. Esidrix induced copious diuresis resulting in almost complete disappearance of edema.

Supplied: Esidrix *Tablets,* 25 mg. (pink, scored) and 50 mg. (yellow, scored); bottles of 100 and 1000.

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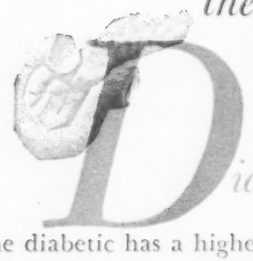
ARDSLEY, NEW YORK

PR-053

A RATIONALE FOR THERAPEUTIC VITAMIN-MINERAL

Subclinical vitamin-mineral deficiency in chronic degenerative disease

Most degenerative disease changes appear to be related to disturbances of cellular nutrition.[1] Subclinical vitamin or mineral deficiencies often occur despite an adequate caloric intake, and the consequent impairment of enzyme systems may injure body tissues.[2] Considerable evidence indicates that the vitamin reserve is frequently lowered to a serious degree in the older age groups most susceptible to degenerative disorders.[3] Older persons also have increased requirements for such minerals as iron, iodine, copper, calcium and zinc.[4,5,6]



the importance of vitamins and minerals in Diabetes mellitus

The diabetic has a higher requirement for the vitamin B-complex (especially nicotinic acid, thiamine, B_{12}, and riboflavin) than the normal individual.[7] Great losses of calcium and potassium may occur during ketosis.[7] Low tissue zinc levels have recently been reported in a series of diabetic patients.[8] Metabolic deficiencies are frequently aggravated by diets which restrict or eliminate foods rich in essential co-factors.[9] Administration of more than normal requirements often produces a decided clinical improvement and may help to prevent neuropathic changes.[7]



the importance of vitamins and minerals in Digestive disorders

Peptic ulcer diets are often deficient in essential vitamins. Symptoms attributable to B-vitamin deficiency are commonly observed in patients on such diets.[10]

Liver damage leads to faulty vitamin metabolism, and cirrhosis often produces severe vitamin deficiency.[11,12] Pollack and Halpern recommend daily administration of therapeutic vitamins to patients with hepatitis or cirrhosis.[11] Large amounts of zinc are also lost by the cirrhotic patient.[13]

Great care must be exercised to avoid excessive depletion of vitamins and minerals in ulcerative colitis, regional enteritis, and chronic diarrhea. Patients with extensive bowel resections may require up to six times the normal daily vitamin requirement.[14]



the importance of vitamins and minerals in Arthritic disorders

According to Spies,[15] nutritive failure is especially frequent in arthritic or rheumatic disorders. Some patients lose the desire to eat; some are too disabled to earn money to purchase required foods; still others are unable to perform all the necessary masticatory motions. Nausea and vomiting may prevent adequate absorption.

Therapeutic vitamins prevent or correct vitamin deficiency in the arthritic on an inadequate diet. In degenerative joint disease, vitamin therapy is recommended even when there is no demonstrable deficiency.[16] Mineral supplementation may help prevent the depletion of calcium and potassium that occurs during therapy with cer-

tain of the adrenal steroids. Iron[17] may be useful in preventing the anemia common in arthritis.



the importance of vitamins and minerals in Other degenerative processes

Vitamins and minerals appear to play a role in many other degenerative processes associated with aging. Studies by Wexberg,[18] Jolliffe[19] and others indicate that many of the symptoms attributed to senility or cerebral arteriosclerosis respond with remarkable speed to the administration of vitamins. Pyridoxine and nicotinic acid may even play an important role in the prevention of atherosclerosis.

Vitamin or mineral deficiency may be an unrecognized factor in still other situations. As Kampmeier states:

"Who can say, for example, whether the patient chronically ill with myocardial failure may not have a poorer myocardium because of a moderate deficiency in the vitamin B-complex? Something is known of the relationship of vitamin C to the intercellular ground substance and repair of tissues. One may speculate upon the effects of a deficiency of this vitamin, short of scurvy, upon the tissues in chronic disease. Are there 'subclinical' degrees of vitamin deficiencies to search for, now that frank deficiency states have become so rare at least in the United States?"[2]

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Each THERAGRAN-M capsule-shaped tablet supplies:

Vitamin A	25,000 U.S.P. units
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Calcium Pantothenate	20 mg.
Vitamin B_{12} Activity Concentrate	5 mcg.
Vitamin K	2 mg.
Vitamin E	5 Int. units
Calcium	105 mg.
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Potassium	5 mg.
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Dosage: 1 tablet daily or as recommended.

Supply: Family Packs of 180.
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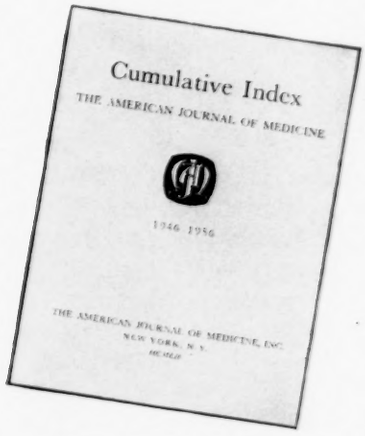
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*Cohen, B. M.: The Ambulatory Patient with Hypertension: An Approach to Office Management, presented at the American Medical Association Convention, San Francisco, California, June 22-27, 1958.

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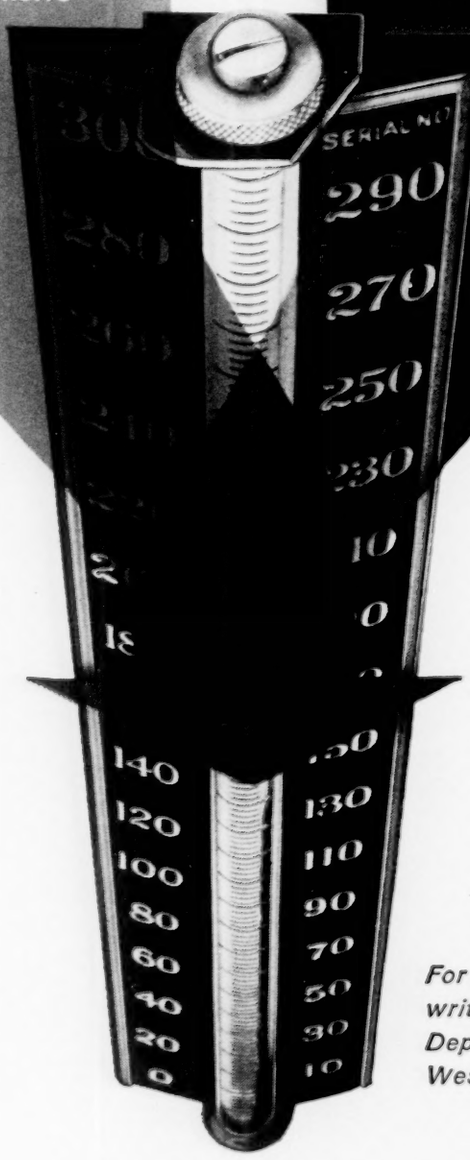
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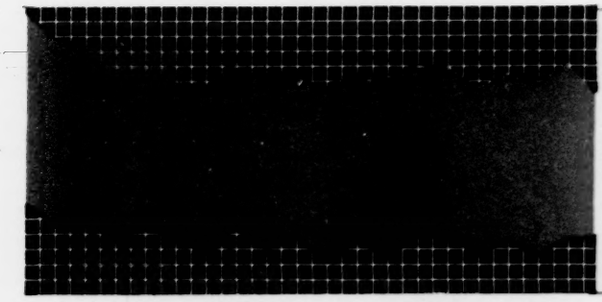
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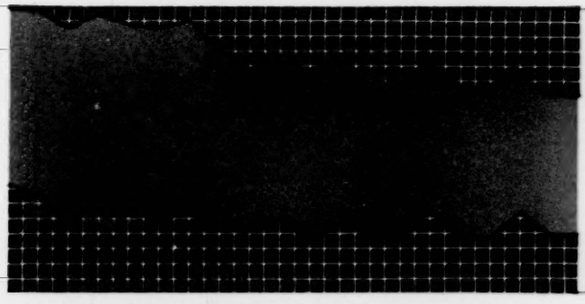
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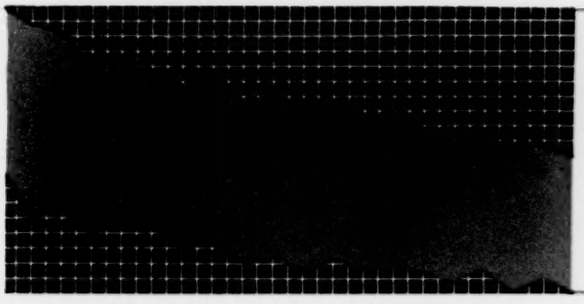
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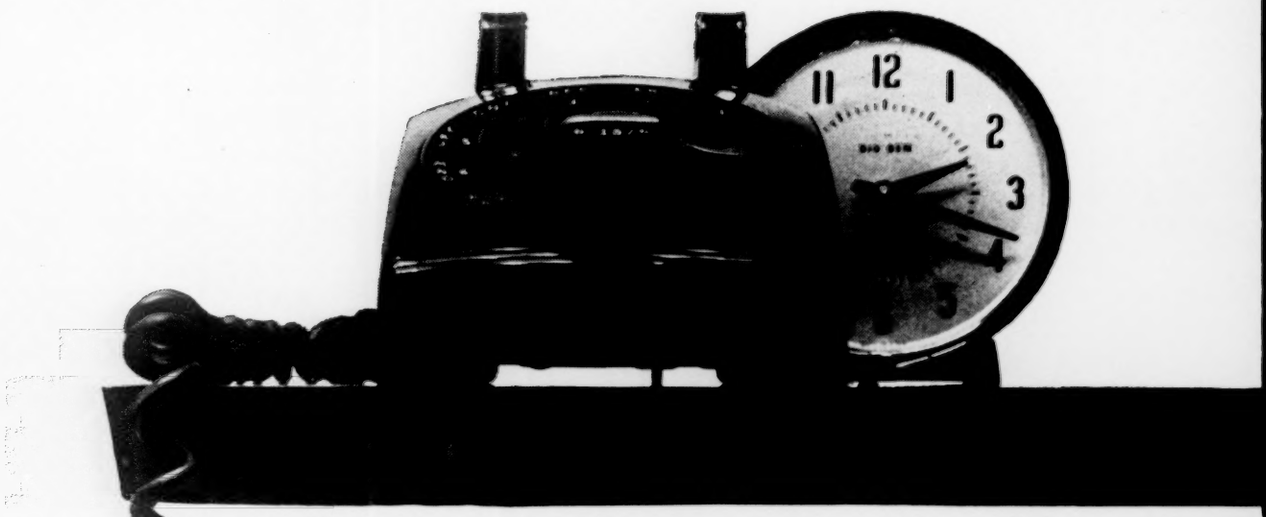
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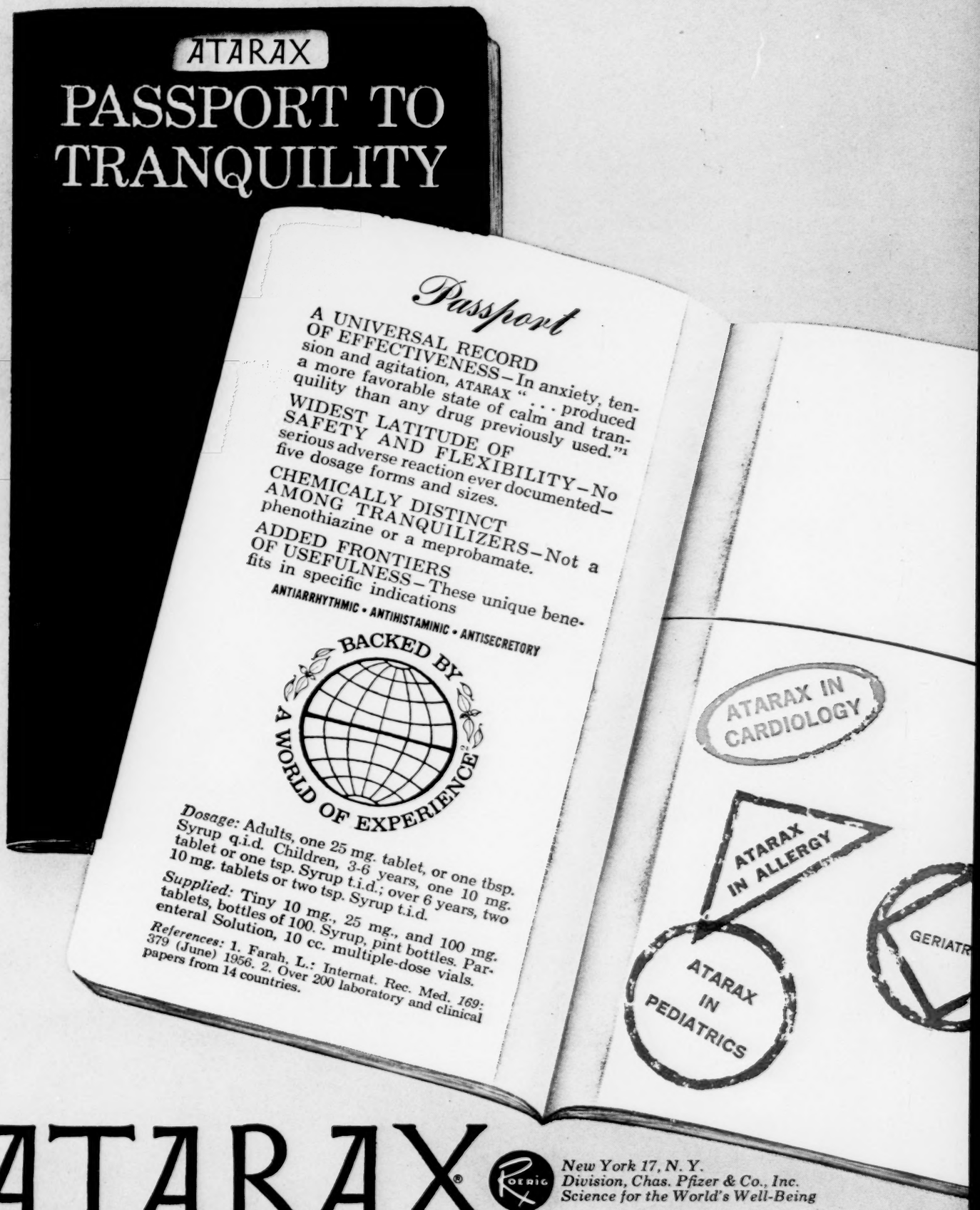
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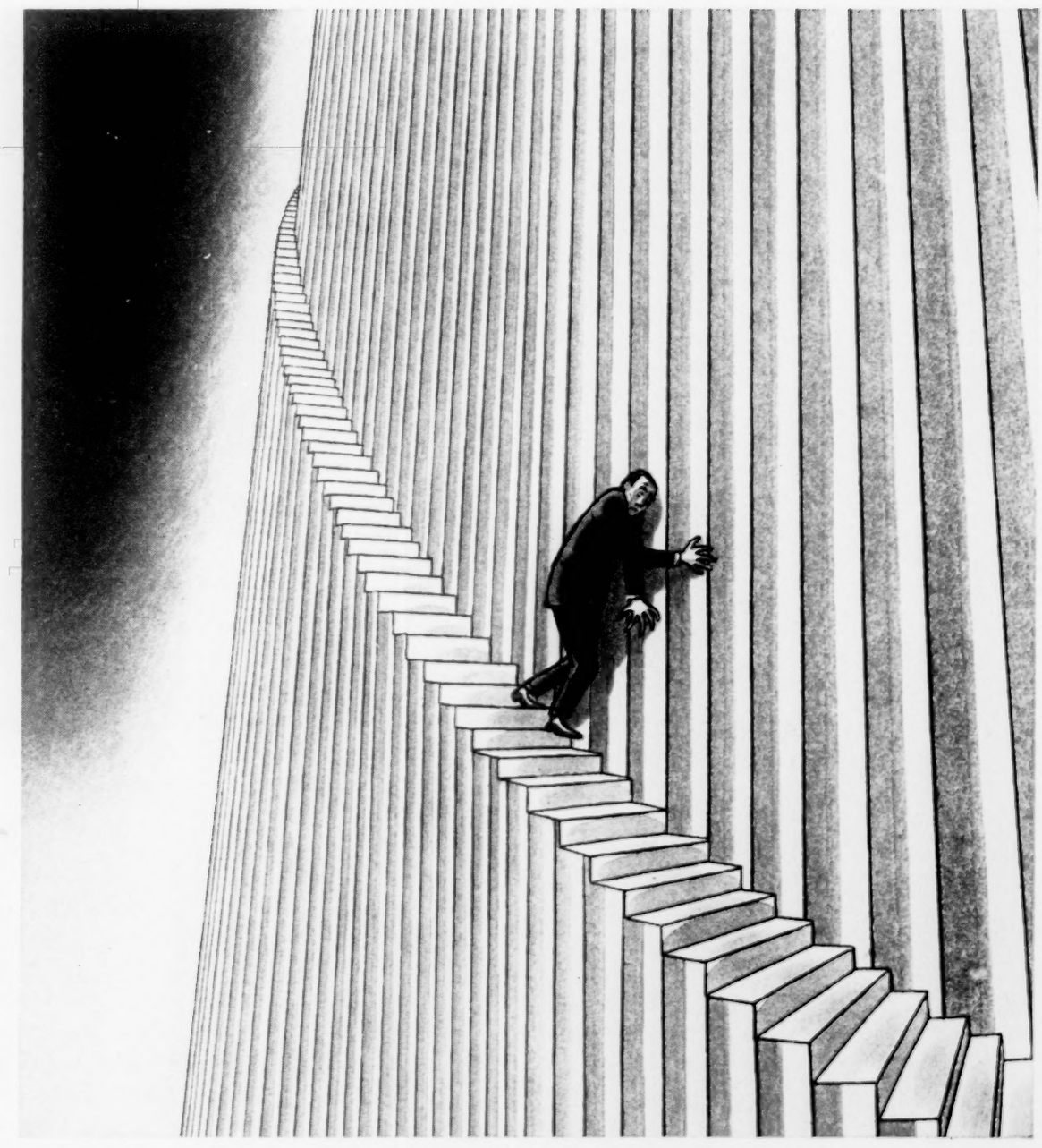
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specific antiemetic antinauseant

no sedative properties
no tranquilizer side effects

Suggested uses: Both prophylactic and therapeutic control of nausea and vomiting associated with pregnancy, travel sickness, gastrointestinal disorders, operative procedures, carcinomatoses, toxicoses, other underlying disease processes, drug administration and radiation therapy.

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References: **1.** W. Schallek, C. A. Heise, E. F. Keith and R. E. Bagdon, *J. Pharmacol. & Exper. Therap.*, in press. **2.** W. B. Abrams, I. Roseff, J. Kaufman, L. Goldman and A. Bernstein, to be published. **3.** I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, *J. Newark Beth Israel Hosp.*, 9:189, 1958. **4.** O. C. Brandman, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. **5.** J. A. Lucinian, *ibid.* **6.** D. W. Molander, *ibid.* **7.** B. I. Shnider, *ibid.* **8.** W. S. Derrick, *ibid.* **9.** B. Wolfson and F. F. Foldes, *ibid.* **10.** L. McLaughlin, *ibid.* **11.** Reports on file, Roche Laboratories. **12.** Personal communications. **13.** W. K. Gauthier, Discussant at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. **14.** H. E. Davis, *ibid.*

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for prompt control of

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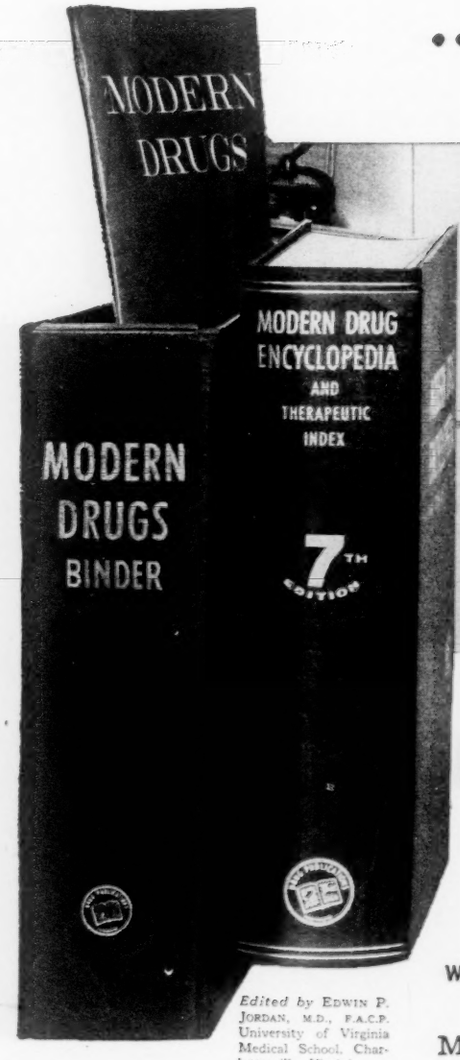
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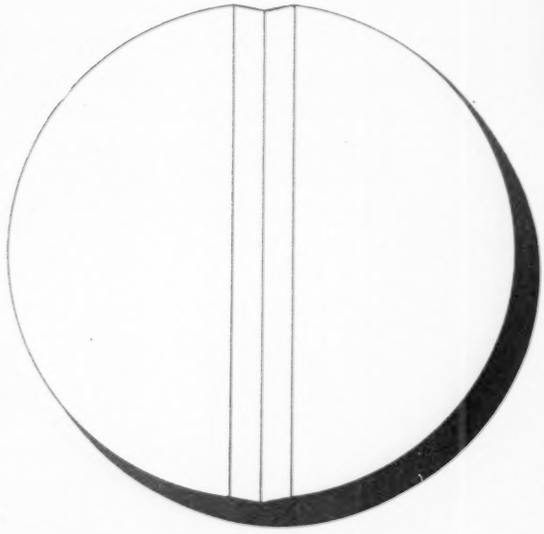
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Q. What is a "neuroleptic" agent?

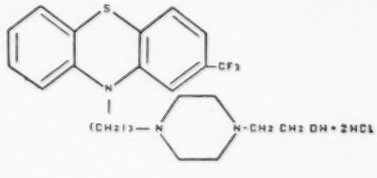
A. The term "neuroleptic" implies a specific effect of a pharmacologic agent on the nervous system. It refers to a mode of action on specific subcortical areas which strongly influence emotional behavior in contradistinction to hypnotic agents which dull the senses. Neuroleptics achieve control of anxiety symptoms without inducing either somnolence or euphoria. Thus, there is an increase in the patient's capacity to cope with life's problems more successfully. The terms "tranquilizers" and "ataraxics" are descriptively impressive, but they fail to convey what seems pharmacologically unique.

Q. Why introduce the term "neuroleptic"?

A. Because it has a precise psychopharmacologic meaning and is more descriptive of the action of PERMITIL than any other current term.

Q. What is PERMITIL?

A. PERMITIL is a new anti-anxiety agent of extraordinary potency and effectiveness. Chemically, PERMITIL is 1-(2-hydroxyethyl)-4-[3-(2-trifluoromethyl-10-phenothiazinyl)-propyl]-piperazine dihydrochloride. The structural formula is:

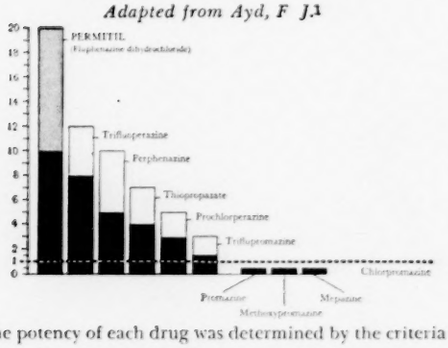


Q. Why is PERMITIL unique?

A. Although PERMITIL can be broadly classified as a phenothiazine, it exhibits a spectrum of unique effects at unprecedented low dosage—a feature that markedly distinguishes this compound from other anti-anxiety drugs.

The Relative Therapeutic Potency of Various Phenothiazines

Adapted from Ayd, F. J.[1]



The potency of each drug was determined by the criteria proposed by Freyhan.[2] These were: *(1)* the attainable level of psychomotor inhibition, *(2)* the speed of action, and *(3)* the dosage required to obtain effective action.

Q. What are the distinctive clinical advantages of PERMITIL?

A. Extensive clinical studies have established important psychopharmacologic advantages for PERMITIL.

1. The effective dosage of PERMITIL *(0.25 mg.* b.i.d.) is the lowest safe dosage of any anti-anxiety agent. Since fractional milligram doses of PERMITIL usually produce a therapeutic effect, many of the annoying side effects of the other phenothiazines, which are dose-related, occur less frequently or not at all. In fact, any side effects associated with dosage not exceeding 1 mg. per day have been uncommon and transitory. PERMITIL represents an advance over its predecessors[1] because of its higher level of therapeutic response and low order of side reactions.

2. Unlike other phenothiazines, PERMITIL alleviates symptoms of anxiety, tension, agitation and emotional unrest *without* depressant effect, impaired alertness or slowed intellectual function. Furthermore, anxiety-induced symptoms of apathy, indifference, listlessness, reduced initiative and chronic emotional fatigue (often refractory to other phenothiazines) frequently respond to administration of PERMITIL. Thus, a significantly wider spectrum of "target symptoms" amenable to therapy is an outstanding property of PERMITIL.

3. Onset of action is rapid and patients soon become more relaxed and less tense. The patient regains a more confident outlook and normal drive is restored.

4. PERMITIL has an inherently long duration of effect. This makes possible a particularly convenient and easy-to-remember schedule of morning and evening dosage.

Q. For what, specifically, is PERMITIL indicated?

A. PERMITIL is indicated for the control of the "target symptoms" of emotional stress so common in everyday office practice. The basic areas of usefulness for PERMITIL are: (1) behavioral disturbances characterized by anxiety, tension, apprehension and instability, as well as depressive symptoms associated with anxiety states; (2) emotional stress accompanying organic disorders and complicating recovery from, or acceptance of, the underlying condition; (3) chronic disorders in which anxiety and stress are contributing factors, e.g., gastrointestinal dysfunctions, neurodermatitis, asthma, premenstrual tension, arthritis, hypertension and tension headache.

Q. Is the dosage schedule, as with many phenothiazine derivatives, complex and complicated?

A. No. PERMITIL has an inherently long duration of effect so that twice-a-day dosage provides the patient with day and night symptom alleviation. The lowest dose of PERMITIL that will produce the desired clinical effect should be used. *The recommended dose for most adults is one 0.25 mg. tablet twice a day.* This may be increased to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms who have had a trial of lower dosages first that were well tolerated but were only partially effective. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. (Dosage for children has not been established.)

Q. What about side effects and contraindications to PERMITIL?

A. At the recommended dosage of PERMITIL, side effects have been observed infrequently or not at all. PERMITIL, as with other phenothiazines, is contraindicated in severely depressed states.

Q. How is PERMITIL supplied?

A. PERMITIL is available as Tablets, 0.25 mg., bottles of 50 and 500.

References: 1. Ayd, F. J.: The current status of major tranquilizers, in press. 2. Freyhan, F. A.: Therapeutic implications of differential effects of new phenothiazine compounds, Am. J. Psychiat. 115:577-585 (Jan.), 1959.

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1. Peck, F.B., Jr., and Griffith, R.S.: Antibiotics Annual 1957-1958, Medical Encyclopedia, Inc., p. 1004. 2. Wright, W.W., and Welch, H.: Antibiotic Med. 5:139 (Feb.) 1958.

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Duke University Hospital, Durham, N. C.

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Nils Nordstrom, Jr., M.D., D.D.S.
Binghamton, N. Y.

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Edward C. Hinds, M.D., D.D.S.
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Neurosurgical Procedures for the Control of Intractable Pain in Malignancies of the Head and Neck
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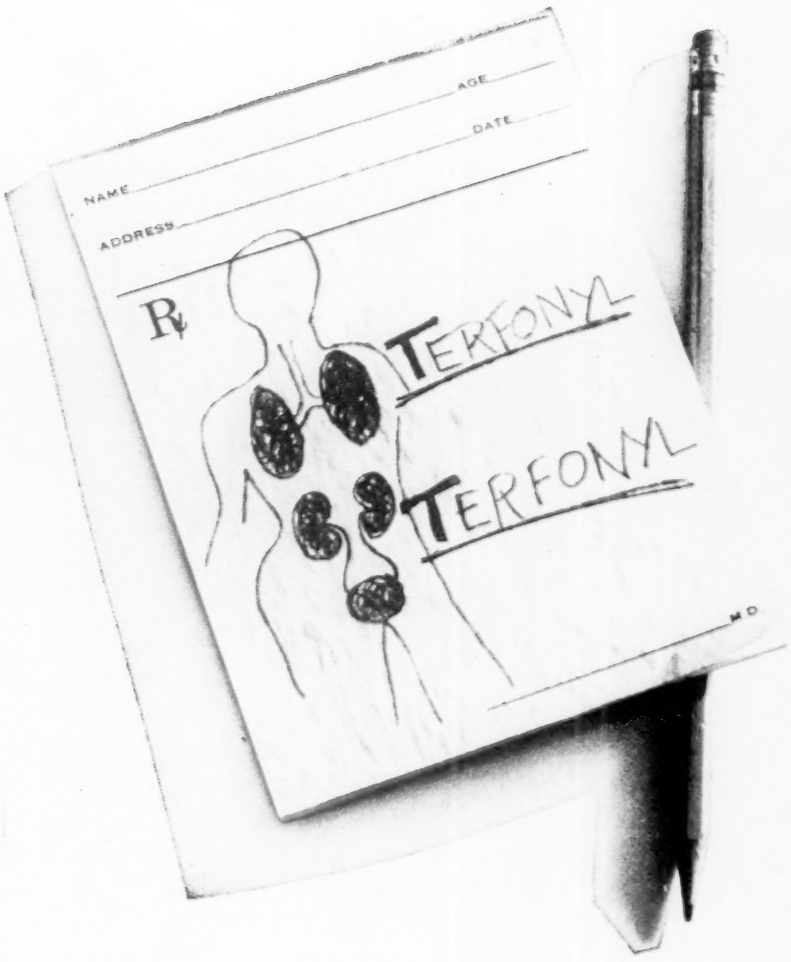
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1. Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Company, 1957, p. 232. 2. Sophian, L. H.; Piper, D. L., and Schneller, G. H.: The Sulfapyrimidines, New York, A. Colish, 1952, pp. 70-76. 3. Lehr, D.: New York J. Med. 50:1361 (June 1) 1950.

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